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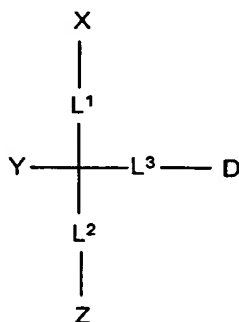
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(54) Title: **POTASSIUM CHANNEL MODULATORS**

WO 03/059873 A1



(I)

(57) Abstract: This invention relates to novel compounds characterized by the general Formula (I) any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, useful as potassium channel modulators. More specifically the invention provides chemical compounds useful as modulators of SK_{Ca} and/or IK_{Ca} channels.

POTASSIUM CHANNEL MODULATORS

TECHNICAL FIELD

5 This invention relates to novel compounds useful as potassium channel modulators. More specifically the invention provides chemical compounds useful as modulators of SK_{Ca} and/or IK_{Ca} channels.

BACKGROUND ART

10

Ion channels are transmembrane proteins, which catalyse the transport of inorganic ions across cell membranes. The ion channels participate in processes as diverse as the generation and timing of action potentials, synaptic transmissions, secretion of hormones, contraction of muscles, etc.

15 Two types of Ca²⁺-activated potassium channels have been described from lymphocytes: 1) Small-conductance, apamin-sensitive, Ca²⁺-activated K-channels (SK_{Ca}) and 2) Intermediate-conductance, inwardly rectifying, Clotrimazole-sensitive, Ca²⁺-activated K-channels (IK_{Ca}), also referred to as Gardos-channels.

20 WO 97/34589 describes triaryl methane compounds that inhibit mammalian cell proliferation, inhibit the Gardos channel of erythrocytes, reduce sickle erythrocyte dehydration and/or delay the occurrence of erythrocyte sickling or deformation, and suggest the use of these compounds in abnormal cell proliferation.

WO 97/34599 describes the use of Clotrimazol and related compounds in the treatment of diarrhoea.

25 WO 00/50026 describes Gardos channel antagonists (i.e. Ca²⁺-activated K-channels), which inhibit the Gardos channel of erythrocytes, reduce sickle erythrocyte dehydration and/or delay the occurrence of erythrocyte sickling or deformation.

30 WO 01/27070 describes the use of carbonylamino derivatives for treating CNS disorders relating to metabotropic glutamate receptor antagonists and/or agonists.

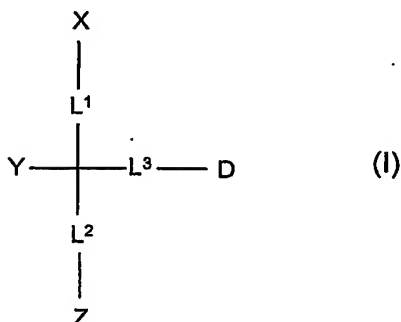
WO 01/49663 describes the use of certain substituted triarylmethane compounds for immunosuppressive treatment of autoimmune disorders or inflammatory diseases.

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SUMMARY OF THE INVENTION

According to the present invention it has now been found that a particular group of chemical compounds possess valuable activity as modulators of SK_{Ca} and/or IK_{Ca} channels.

In its first aspect the invention provides chemical compounds characterized by the general Formula I



any of its enantiomers or any mixture of its enantiomers, or a
 5 pharmaceutically acceptable salt thereof, or an N-oxide thereof,
 wherein

X and Y, independently of each another, represent a mono- or polycyclic, carbocyclic and/or heterocyclic group, which carbocyclic or heterocyclic groups optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy,
 10 alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, alkoxy-alkoxy-carbonyl, a malonic acid dialkyl ester, a diphenyl methyl group, or a mono- or polycyclic, carbocyclic or
 15 heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

L^1 and L^2 , independently of each another, may be absent or represent divalent alkyl, alkenyl, alkynyl, O, S or NR^9 ; wherein

20 R^9 represents hydrogen, alkyl, alkoxy or aryl; and

L^3 may be absent or represents a linker of the formula $-(CH_2)_n-Y-(CH_2)_m-$,
 wherein

n and m, independently of each another, represent 0, 1, 2, 3 or 4; and

Y is absent or represents O, S, NR^9 , wherein

25 R^9 represents hydrogen, alkyl, alkoxy or aryl; and

D represents alkyl, cycloalkyl, alkenyl, alkynyl or haloalkyl, or a group of the formula $-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$, $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$, $-R^6-NR^5S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-NR^5C(=O)R^4$,

$-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$,
 $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or
 $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl,
 5 alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be
 substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a
 heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl,
 10 cycloalkyl, aryl and heteroaryl; or

D represents a mono- or polycyclic, carbocyclic or heterocyclic group, which
 carbocyclic or heterocyclic group optionally may be substituted one or more times with
 alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl and heteroaryl, and/or a
 group of the formula $-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$,
 15 $-R^6-S(=O)R^4$, $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$,
 $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$,
 $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$,
 $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-C(=O)NR^5R^4$,
 20 $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$,
 $-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$,
 $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl,
 alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be
 25 substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a
 heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl,
 cycloalkyl, aryl and heteroaryl; or

30 D represents $-S-R^1$, $-S(=O)-R^1$, $-S(=O)_2-R^1$, $-S(=O)-NR^2R^3$, $-S-C(=O)-R^1$, $-S-$
 $C(=O)-NR^2R^3$, $-O(C=O)-R^1$, $-O(C=O)-NR^2R^3$, $-N(C=O)-R^1$, $-N(C=O)-NR^2R^3$, $-P-(R^2R^3)$,
 $-P(=O)-R^1$, $-P(=O)-(R^2R^3)$, $-P(=O)_2-(R^2R^3)$; wherein

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, haloalkyl,
 aryl, aralkyl, heteroaryl or heteroaryl-alkyl, which aromatic groups may optionally be
 35 substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or a group of the
 formula $-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$,
 $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$,

$-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$,
 $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-NR^5C(=O)R^4$,
 $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$,
 $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or
 5 $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a
 10 heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen, hydroxy, alkyl or alkoxy; or

15 R^2 and R^3 , together with the phosphor atom to which they are bound, represent a heterocyclic ring; or

R^1 represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl, heteroaryl and/or
 20 a group of the formula $-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$,
 $-R^6-S(=O)R^4$, $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$,
 $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$,
 $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$,
 25 $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-C(=O)NR^5R^4$,
 $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$,
 $-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$,
 $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl,
 30 alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl,
 35 cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen, alkyl or alkoxy.

In another aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of a chemical compound of the

invention, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

In yet another aspect the invention relates to the use of a chemical compound of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a medicament.

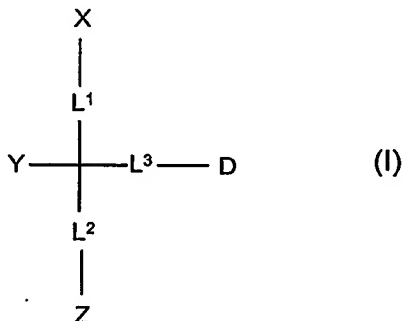
In still another aspect the invention provides methods for treatment, prevention or alleviation of diseases or disorders or conditions responsive to modulation of SK_{Ca} and/or IK_{Ca} channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention or a pharmaceutically-acceptable addition salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Tertiary Triaryl Derivatives

In its first aspect the present invention provides tertiary triaryl derivative of Formula I



an enantiomer or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof,

wherein

X and Y, independently of each another, represent a mono- or polycyclic, carbocyclic and/or heterocyclic group, which carbocyclic or heterocyclic groups optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, alkoxy-alkoxy-carbonyl, a malonic acid dialkyl ester, a diphenyl methyl group, or a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be

substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

L^1 and L^2 , independently of each another, may be absent or represent divalent alkyl, alkenyl, alkynyl, O, S or NR^9 ; wherein

5 R^9 represents hydrogen, alkyl, alkoxy or aryl; and

L^3 may be absent or represents a linker of the formula $-(CH_2)_n-Y-(CH_2)_m-$, wherein

n and m , independently of each another, represent 0, 1, 2, 3 or 4; and

Y is absent or represents O, S, NR^9 , wherein

10 R^9 represents hydrogen, alkyl, alkoxy or aryl; and

D represents alkyl, cycloalkyl, alkenyl, alkynyl or haloalkyl, or a group of the formula

15 $-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$,
 $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$,
 $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$,
 $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-NR^5C(=O)R^4$,
 $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$,
20 $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or
 $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

25 R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

D represents a mono- or polycyclic, carbocyclic or heterocyclic group, which
30 carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl and heteroaryl, and/or a group of the formula

35 $-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$,
 $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$,
 $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$,
 $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-C(=O)NR^5R^4$,
 $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$,

$-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$,
 $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

10 D represents $-S-R^1$, $-S(=O)-R^1$, $-S(=O)_2-R^1$, $-S(=O)-NR^2R^3$, $-S-C(=O)-R^1$, $-S-C(=O)-NR^2R^3$, $-O(C=O)-R^1$, $-O(C=O)-NR^2R^3$, $-N(C=O)-R^1$, $-N(C=O)-NR^2R^3$, $-P-(R^2R^3)$, $-P(=O)-R^1$, $-P(=O)-(R^2R^3)$, $-P(=O)_2-(R^2R^3)$; wherein

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, heteroaryl or heteroaryl-alkyl, which aromatic groups may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or a group of the formula

20 $-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$,
 $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$,
 $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$,
 $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-NR^5C(=O)R^4$,
 $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$,
 $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or
25 $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

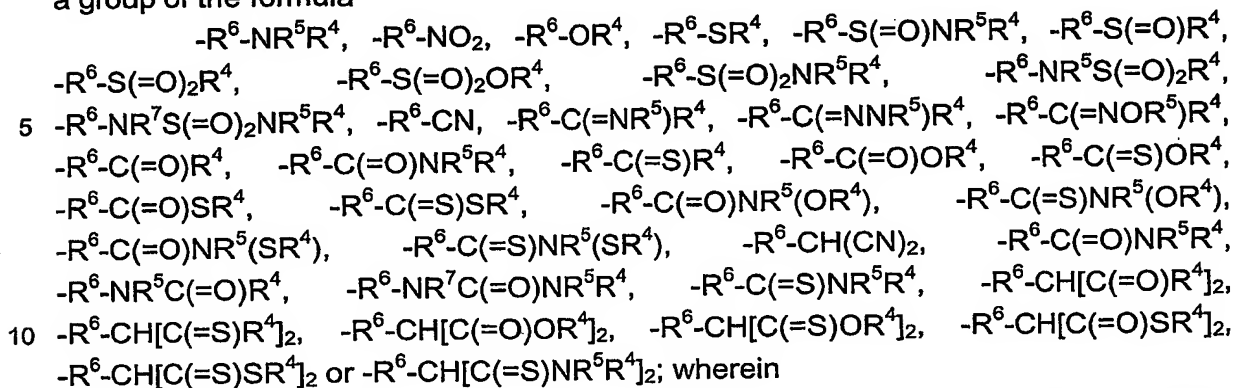
30 R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen, hydroxy, alkyl or alkoxy; or

35 R^2 and R^3 , together with the phosphor atom to which they are bound, represent a heterocyclic ring; or

R^1 represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more

times with alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl, heteroaryl and/or a group of the formula



R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with with halogen, alkyl, CF_3 , nitro and/or cyano; or

15 R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

20 R^2 and R^3 , independently of each another, represent hydrogen, alkyl or alkoxy.

In a more preferred embodiment

L^1 and L^2 are absent; and

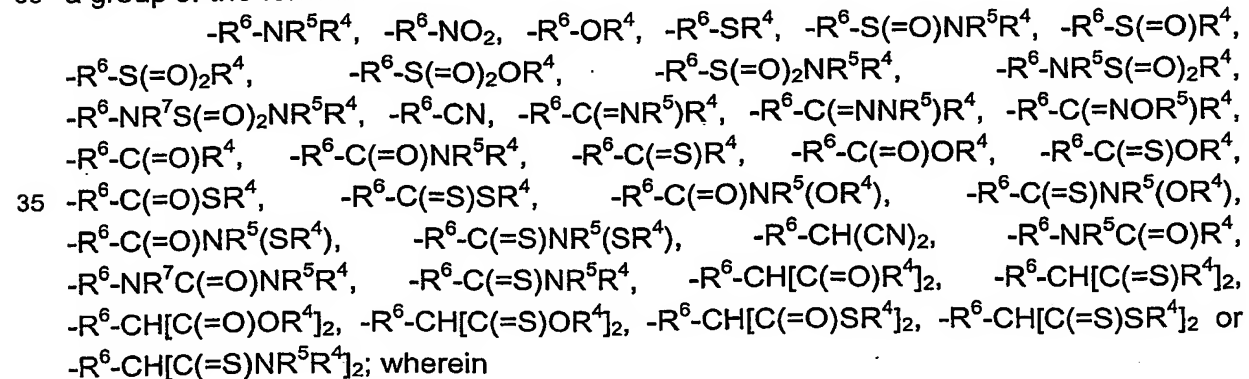
L^3 is absent or represents a linker of the formula $-Y-$, wherein

Y represents O, S or NR^9 , wherein

25 R^9 represents hydrogen or alkyl; and

D represents $-S-R^1$, $-S(=O)-R^1$, $-S(=O)_2-R^1$, $-S(=O)-NR^2R^3$, $-S-C(=O)-R^1$, $-S-C(=O)-NR^2R^3$, $-O(C=O)-R^1$, $-O(C=O)-NR^2R^3$, $-N(C=O)-R^1$, $-N(C=O)-NR^2R^3$, $-P-(R^1)_2$, $-P(R^2R^3)$, $-P(=O)-R^1$, $-P(=O)-(R^2R^3)$, $-P(=O)_2-(R^1)_2$ or $-P(=O)-(OR^1)_2$; wherein

30 R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, haloalkyl, or a group of the formula



R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen, hydroxy, alkyl or alkoxy; or

R^2 and R^3 , together with the phosphor atom to which they are bound, represent a heterocyclic ring; or

R^1 represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl, heteroaryl and/or a group of the formula

$-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$, $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$, $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$, $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-C(=O)NR^5R^4$, $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen or alkyl.

In a yet more preferred embodiment,

X, Y and Z represent a phenyl group, which phenyl groups, independently of each another, are optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

X and Y represent a phenyl group, which phenyl groups, independently of each another, are optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, halo-alkyl, halo-alkenyl, halo-alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, alkoxy-alkoxy-carbonyl, a malonic acid dialkyl ester or a diphenyl methyl group; or

5 X and Y represent a phenyl group, which phenyl groups, independently of each another, are optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

Z represents a heteroaryl group, which heteroaryl is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen,
10 haloalkyl, nitro and/or cyano; or

one of X and Y represents a phenyl group, which phenyl group is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

the other of X and Y represents a heteroaryl group, which heteroaryl is
15 optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, halo-alkyl, halo-alkenyl, halo-alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, alkoxy-alkoxy-carbonyl, a malonic
20 acid dialkyl ester or a diphenyl methyl group; or

one of X and Y represents a phenyl group, which phenyl group is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

Z and the other of X and Y represents a heteroaryl group, which heteroaryl
25 is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

In an even more preferred embodiment, the heteroaryl group is thiazolyl, in particular 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in
30 particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl, [1,3,2]dioxaphospholane or [1,3,2]dioxaphosphinane.

In a still more preferred embodiment

X, Y and Z represent a phenyl group, which phenyl groups, independently
35 of each another, optionally are substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; or

X and Y represent a phenyl group, which phenyl groups, independently of each another, optionally are substituted one or more times with halogen, in particular

fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-
5 carbonyl, malonic acid dialkyl ester or a diphenyl methyl group; or

X and Y represent a phenyl group, which phenyl groups, independently of each another, optionally are substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano; and

10 Z represents 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl, 2-pyridinyl or [1,3,2]dioxaphospholane, which aromatic groups may be substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano; or

one of X and Y represents a phenyl group, which phenyl group is optionally
15 substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano; and

the other of X and Y represents 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl, 2-pyridinyl or [1,3,2]dioxaphospholane, which aromatic groups may be
20 substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-
25 carbonyl, malonic acid dialkyl ester or a diphenyl methyl group; or

one of X and Y represents a phenyl group, which phenyl group is optionally substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano; and

30 Z and the other of X and Y represents 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl, 2-pyridinyl or [1,3,2]dioxaphospholane, which aromatic groups may be substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano.

35 In a still more preferred embodiment

D represents a phenyl group, which phenyl group is substituted once or twice with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano; or

D represents a heteroaryl group selected from 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl or 2-pyridinyl, which heteroaryl group may be substituted once or twice with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; hydroxy, nitro and/or cyano;
 5 and

L³ is absent or represents a linker of the formula -Y-, wherein

Y represents O or S.

In a still more preferred embodiment the phenyl groups and/or the heteroaryl groups are substituted once or twice with fluoro, chloro, CF₃, nitro and/or
 10 cyano.

In a most preferred embodiment the compound of the invention is
 2-[Bis-(4-fluoro-phenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-thiazole;
 2-[Tris-(4-fluoro-phenyl)-methylsulfanyl]-pyridin-1-ol;
 1-Methyl-2-[tris-(4-fluoro-phenyl)-methylsulfanyl]-1*H*-imidazole;
 15 2-[Tris-(4-fluoro-phenyl)-methylsulfanyl]-pyridine;
 2-[(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methoxy]-[1,3,2]-

dioxaphospholane; or

2-[Tris-(4-fluoro-phenyl)-methoxy]-[1,3,2]-dioxaphospholane;

any of its enantiomers or any mixture of enantiomers, or a pharmaceutically
 20 acceptable salt thereof, or an N-oxide thereof.

In a still more preferred embodiment

D represents -CN, R⁶-CN, -CON(R²R³), -S-R¹, -S(=O)-R¹, -S(=O)₂-R¹, -S-C(=O)-R¹, -O(C=O)-R¹, -P-(R²R³), -P(=O)(R²R³), -P(=O)₂(R²R³); wherein

R¹ represents alkyl, cycloalkyl, cycloalkyl-alkyl or -NR⁵R⁴; wherein

25 R⁴ and R⁵, independently of each another, represent hydrogen, alkyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R⁴ and R⁵, together with the N atom to which they are bound, form a pyrrolidine or piperidine ring; or

30 R¹ represents aryl, aralkyl, heteroaryl, heteroaryl-alkyl, which aromatic groups may optionally be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; and

R² and R³, independently of each another, represent hydrogen, alkyl or alkoxy; or

35 R² and R³, together with the phosphor atom to which they are bound, represent a heterocyclic ring selected from [1,3,2]dioxaphospholane and [1,3,2]dioxaphosphinane; and

R⁶ is absent or represents alkyl.

In a still more preferred embodiment

L^3 is absent or represents -O- or -S-.

In a still more preferred embodiment X and Y represent a phenyl group, which phenyl groups, independently of each another, optionally are substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF_3 ; nitro and/or cyano;

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, malonic acid dialkyl ester or a diphenyl methyl group; and

D represents -CN, R^6 -CN, $-CON(R^2R^3)$, wherein

R^2 and R^3 , independently of each another, represent hydrogen or alkyl; and R^6 represents alkyl.

In a most preferred embodiment compound of the invention is

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-enenitrile;

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3-methyl-butyronitrile;

2,2-Bis-(4-fluoro-phenyl)-3-methyl-butyronitrile;

2,2-Bis-(4-fluoro-phenyl)-4-methyl-pentanenitrile;

2,2-Bis-(4-fluoro-phenyl)-pent-4-enenitrile;

2,2-Bis-(4-fluoro-phenyl)-pent-4-ynenitrile;

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-ynenitrile;

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-4-methyl-pentanenitrile;

2,2-Bis-(4-fluoro-phenyl)-3,3-diphenyl-propionitrile;

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3,3-diphenyl-propionitrile;

2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3-methyl-butyronitrile;

2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-4-methyl-pentanenitrile;

2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-enenitrile;

2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-ynenitrile;

2,2-Bis-(4-fluoro-phenyl)-3-oxo-butyronitrile;

3-Ethoxy-2-(4-fluoro-phenyl)-2-(2-fluoro-phenyl)-propionitrile;

3-Cyano-3-(4-fluoro-phenyl)-3-(2-fluoro-phenyl)-propionic acid ethyl ester;

3-Ethoxy-2,2-bis-(4-fluoro-phenyl)-propionitrile;

3-Cyano-3,3-bis-(4-fluoro-phenyl)-propionic acid ethyl ester;

Cyano-(4-fluoro-phenyl)-(2-fluoro-phenyl)-acetic acid methyl ester;

2-[Cyano-bis-(4-fluoro-phenyl)-methyl]-malonic acid diethyl ester;

2,2-Bis-(4-fluoro-phenyl)-4-hydroxy-butyronitrile;

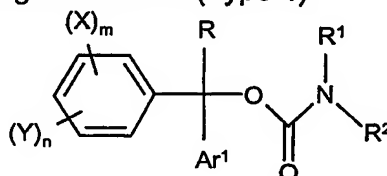
2,2-Bis-(4-fluoro-phenyl)-3-(2-methoxy-ethoxy)-propionitrile;

2,2-Bis-(4-fluoro-phenyl)-succinonitrile; or

2,2-Bis-(4-fluoro-phenyl)-3-methyl-butyramide;

any of its enantiomers or any mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

In a second preferred embodiment, the chemical compound of the invention is represented by the following Formula IV (Type 4)



wherein

m is 0, 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen or alkyl; or

R¹ and R², together with the N atom to which they are bound, form a 5- to 7-membered heterocyclic ring.

In a more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-

imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, 5 halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R^1 and R^2 , independently of each another, represent hydrogen or alkyl; or

R^1 and R^2 , together with the N atom to which they are bound, form a 10 pyrrolidine or a piperidine ring.

In a yet more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF_3 , nitro 15 and/or cyano;

Ar^1 represents phenyl, which may be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano;

Ar^2 represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be 20 substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R^1 and R^2 , independently of each another, represent hydrogen or alkyl; or

R^1 and R^2 , together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

25 In a still more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF_3 , nitro and/or cyano;

30 Ar^1 represents phenyl, which may be substituted once or twice with fluoro, chloro, CF_3 , nitro and/or cyano;

Ar^2 represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, CF_3 , nitro and/or cyano; or

35 R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and

R^1 and R^2 , independently of each another, represent hydrogen or alkyl; or

R^1 and R^2 , together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

In a most preferred embodiment the chemical compound of the invention is

(±)-Carbamic acid tris-(4-fluorophenyl)-methyl ester;
 (±)-Carbamic acid cyclohexyl-bis-(4-fluorophenyl)-methyl ester;
 (±)-Carbamic acid cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methyl ester;
 (±)-Piperidine-1-carboxylic acid tris-(4-fluorophenyl)-thiazol-2-yl-methyl

5 ester;

(±)-Methyl-carbamic acid cyclopentyl-bis-(4-fluorophenyl)-methyl ester;
 (±)-Pyrrolidine-1-carboxylic acid cyclohexyl-bis-(4-fluorophenyl)-methyl

ester;

(±)-Methyl-carbamic acid tris-(4-fluorophenyl)-methyl ester;

10 (±)-Methyl-carbamic acid cyclohexyl-(2-fluorophenyl)-(4-fluorophenyl)-
 methyl ester;

(±)-Carbamic acid cyclohexyl-(4-fluorophenyl)-pyridin-2-yl-methyl ester;

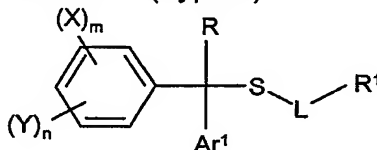
(±)-Dimethyl-carbamic acid tris-(4-fluorophenyl)-methyl ester;

(±)-Carbamic acid (2-fluorophenyl)-bis-(4-fluorophenyl)-methyl ester; or

15 (±)-Carbamic acid (2-fluorophenyl)-(4-fluorophenyl)-phenyl-methyl ester;

an enantiomer or a mixture of enantiomers, or a pharmaceutically
 acceptable salt thereof, or an N-oxide thereof.

In a third preferred embodiment the chemical compound of the invention is
 represented by the following Formula V (Type 5)



20

wherein

n is 1 or 2;

m is 0, 1 or 2;

25 X and Y, independently of each another, represent alkyl, alkenyl, alkynyl,
 amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group,
 which carbocyclic or heterocyclic group optionally may be substituted one or more
 times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
 and/or cyano; and

30 R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or
 heterocyclic group, which carbocyclic or heterocyclic group optionally may be
 substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
 halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkenyl
 35 or halo-alkynyl; and

L is absent or represents alkyl; and

R^1 represents alkyl, cycloalkyl or cycloalkyl-alkyl, $-\text{CN}$, $-\text{C}(=\text{O})\text{OR}^4$, $-\text{C}(=\text{O})\text{N}(\text{R}^4\text{R}^5)$, $-\text{C}(=\text{S})\text{N}(\text{R}^4\text{R}^5)$, wherein R^4 and R^5 , independently of each other, represent hydrogen, alkyl or phenyl, or R^4 and R^5 , together with the nitrogen atom form a heterocyclic ring selected from pyrrolidinyl and piperidinyl, or a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

In a more preferred embodiment

n is 1;

10 m is 0 or 1;

X and Y , independently of each other, represent halogen, alkyl, CF_3 , nitro and/or cyano;

Ar^1 represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-
15 imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

20 Ar^2 represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group
25 may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkenyl or halo-alkynyl; and

L is absent or represents alkyl; and

30 R^1 represents alkyl, cycloalkyl or cycloalkyl-alkyl, $-\text{CN}$, $-\text{C}(=\text{O})\text{OR}^4$, $-\text{C}(=\text{O})\text{N}(\text{R}^4\text{R}^5)$, $-\text{C}(=\text{S})\text{N}(\text{R}^4\text{R}^5)$, wherein R^4 and R^5 , independently of each other, represent hydrogen, alkyl or phenyl, or R^4 and R^5 , together with the nitrogen atom form a heterocyclic ring selected from pyrrolidinyl and piperidinyl, or an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl;
35 imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

In a yet more preferred embodiment

m is 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro
5 and/or cyano;

Ar¹ represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl or 2-pyridinyl, which aromatic group may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl or cycloalkyl-alkyl; and

L is absent or represents methylene or ethylene; and

R¹ represents alkyl, cycloalkyl or cycloalkyl-alkyl, -CN, -C(=O)OR⁴,
15 -C(=O)N(R⁴R⁵), -C(=S)N(R⁴R⁵), wherein R⁴ and R⁵, independently of each another, represent hydrogen, alkyl or phenyl, or R⁴ and R⁵, together with the nitrogen atom form a heterocyclic ring selected from pyrrolidinyl and piperidinyl, or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro
20 and/or cyano.

In a still more preferred embodiment

m is 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro
25 and/or cyano;

Ar¹ represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl or 2-pyridinyl, which aromatic group may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and

L is absent or represents -CH₂-; and

R¹ represents cycloalkyl or cycloalkyl-alkyl, -CN, -C(=O)OR⁴,
35 -C(=O)N(R⁴R⁵), -C(=S)N(R⁴R⁵), wherein R⁴ and R⁵, independently of each another, represent hydrogen, alkyl or phenyl, or R⁴ and R⁵, together with the nitrogen atom form a heterocyclic ring selected from pyrrolidinyl and piperidinyl, or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl,

which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano.

In a most preferred embodiment the chemical compound of the invention is

2-[Cyclohexyl-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfanyl]-thiazole;

5 2-[(2-Chlorophenyl)-cyclohexyl-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfanyl]-1-methyl-1*H*-imidazole;

2-[(4-Chlorophenylsulfanyl)-cyclopentyl-(4-fluorophenyl)-(2-fluorophenyl)-methyl]-pyridine;

2-[Cyclohexyl-(3,4-dichlorophenyl)-(1*H*-imidazol-2-yl)-methylsulfanyl]-pyridine;

2-[Cyclopentyl-(2-fluorothiazol-4-yl)-(4-nitro-3-trifluoromethylphenyl)-methylsulfanyl]-pyridine;

2-[(4-fluorophenyl)-(4-fluorophenylsulfanyl)-(4-nitro-3-trifluoromethylphenyl)-methyl]-thiazole;

15 2-[Cyclohexylsulfanyl-(4-fluorophenyl)-(4-nitro-3-trifluoromethylphenyl)-methyl]-thiazole;

2-[Cyclopentylsulfanyl-bis-(4-fluorophenyl)-methyl]-1-methyl-1*H*-imidazole;

4-[Cyclohexylsulfanyl-bis-(4-fluorophenyl)-methyl]-2-fluoro-thiazole;

2-[Bis-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfonyl]-thiazole;

20 1-Methyl-2-[tris-(4-fluorophenyl)-methylsulfanyl]-1*H*-imidazole;

2-[Tris-(4-fluorophenyl)-methylsulfanyl]-pyridine;

2-[Tris-(4-fluorophenyl)-methylsulfanyl]-pyridine-N-oxide;

[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-acetonitrile;

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-acetamide;

25 [(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methylsulfanyl]-acetic acid;

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-propionamide;

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-thioacetamide;

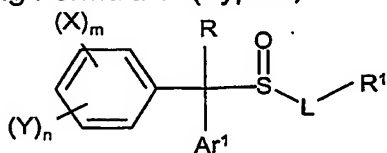
2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-*N,N*-diethyl-

acetamide; or

30 2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-1-piperidin-1-yl-ethanone;

an enantiomer or a mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

In a fourth preferred embodiment the chemical compound of the invention is represented by the following Formula VI (Type 6)



wherein

m is 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl,
5 amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group,
which carbocyclic or heterocyclic group optionally may be substituted one or more
times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
and/or cyano; and

10 R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or
heterocyclic group, which carbocyclic or heterocyclic group optionally may be
substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl,
15 halo-alkenyl or halo-alkynyl; and

L is absent or represents alkyl; and

R¹ represents cycloalkyl, or a mono- or polycyclic, carbocyclic or
heterocyclic group, which carbocyclic or heterocyclic group optionally may be
substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
20 halogen, haloalkyl, nitro and/or cyano.

In a more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro
25 and/or cyano;

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl;
isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-
imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-
isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-
30 pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group
may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
halogen, haloalkyl, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl;
isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-
35 imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-
isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-
pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group
may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

L is absent or represents alkyl; and

R¹ represents cycloalkyl or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano.

In a yet more preferred embodiment

m is 0 or 1;

n is 0 or 1;

10 X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro and/or cyano;

Ar¹ represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

15 Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl; and

L is absent or represents methylene or ethylene; and

20 R¹ represents cycloalkyl or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, methyl, CF₃, nitro and/or cyano.

In a still more preferred embodiment

m is 0 or 1;

25 n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

30 Ar¹ represents an aromatic group selected from phenyl and 2-thiazolyl, which aromatic groups may be substituted once or twice with fluoro, CF₃, nitro and/or cyano;

Ar² represents phenyl, which may be substituted once or twice with fluoro, CF₃, nitro and/or cyano; or

R represents cycloalkyl or cycloalkyl-alkyl; and

L is absent or represents -CH₂-; and

35 R¹ represents cycloalkyl, phenyl, 2-thiazolyl, 2-imidazolyl or 2-pyridinyl, which aromatic groups may be substituted once with fluoro, CF₃, nitro and/or cyano; or

R¹ represents 2-thiazolyl-methyl.

In a most preferred embodiment the chemical compound of the invention is Methyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-1);

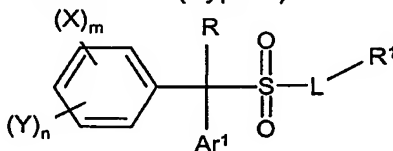
Ethyl (bis(4-fluorophenyl)phenyl)methyl sulfoxide (Compound 6-2);
 Cyclohexylmethyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-3);
 Cyclohexyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-4);
 Isopropyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-5);
 5 (2-Thiazolyl)methyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-6);
 Phenyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-7);
 1-Methyl-2-imidazolyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-8);
 2-Pyridyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-9);
 (Cyclohexyl-bis(4-fluorophenyl))methyl phenyl sulfoxide (Compound 6-10);
 10 (Cyclopentyl-bis(4-fluorophenyl))methyl methyl sulfoxide (Compound 6-11);

or

(Cyclohexyl-(4-fluorophenyl)-(2-thiazolyl))methyl methyl sulfoxide
 (Compound 6-12);

an enantiomer or a mixture of enantiomers, or a pharmaceutically
 15 acceptable salt thereof, or an N-oxide thereof.

In a fifth preferred embodiment the chemical compound of the invention is
 represented by the following Formula VII (Type 7)



wherein

20 m is 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl,
 hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group,
 25 which carbocyclic or heterocyclic group optionally may be substituted one or more
 times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
 and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or
 heterocyclic group, which carbocyclic or heterocyclic group optionally may be
 30 substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
 halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl,
 halo-alkenyl or halo-alkynyl; and

L may be absent or represents alkyl; and

35 R¹ represents alkyl, cycloalkyl or a mono- or polycyclic, carbocyclic or
 heterocyclic group, which carbocyclic or heterocyclic group optionally may be

substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

In a more preferred embodiment

m is 1;

5 n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-
10 imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

15 Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group
20 may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

L may be absent or represents alkyl; and

25 R¹ represents alkyl, cycloalkyl or an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl;
30 which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

In a yet more preferred embodiment

m is 1;

n is 0 or 1;

35 X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro and/or cyano;

Ar¹ represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl; and

5 L may be absent or represents methylene or ethylene; and

R¹ represents alkyl, cycloalkyl or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano.

In a still more preferred embodiment

10 m is 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro and/or cyano;

15 Ar¹ represents an aromatic group selected from phenyl and 2-thiazolyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano;

Ar² represents phenyl, which may be substituted once or twice with fluoro, CF₃, nitro and/or cyano; or

R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and

20 L may be absent or represents methylene; and

R¹ represents alkyl or cycloalkyl; or

R¹ represents phenyl, 2-thiazolyl, 2-imidazolyl or 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano.

25 In a most preferred embodiment the chemical compound of the invention is Methyl tris(4-fluorophenyl)methyl sulfone (Compound 7-1);

Ethyl (bis(4-fluorophenyl)phenyl)methyl sulfone (Compound 7-2);

Cyclohexylmethyl tris(4-fluorophenyl)methyl sulfone (Compound 7-3);

Cyclohexyl tris(4-fluorophenyl)methyl sulfone (Compound 7-4);

30 Isopropyl tris(4-fluorophenyl)methyl sulfone (Compound 7-5);

(2-Thiazolyl)methyl tris(4-fluorophenyl)methyl sulfone (Compound 7-6);

Phenyl tris(4-fluorophenyl)methyl sulfone (Compound 7-7);

1-Methyl-2-imidazolyl tris(4-fluorophenyl)methyl sulfone (Compound 7-8);

2-Pyridyl tris(4-fluorophenyl)methyl sulfone (Compound 7-9);

35 (Cyclohexyl-bis(4-fluorophenyl))methyl phenyl sulfone (Compound 7-10);

(Cyclopentyl-bis(4-fluorophenyl))methyl methyl sulfone (Compound 7-11);

(Cyclohexyl-(4-fluorophenyl)-(2-thiazolyl))methyl methyl sulfone (Compound

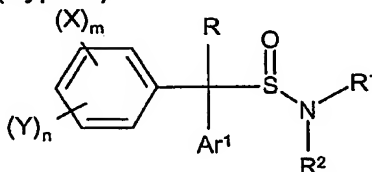
7-12);

((2-Fluorophenyl)-bis(4-fluorophenyl)-phenyl)methyl methyl sulfone
(Compound 7-13); or

Methanesulphonyl-2-fluorophenyl-bis-(4-fluoro-phenyl) methane;

an enantiomer or a mixture of enantiomers, or a pharmaceutically
5 acceptable salt thereof, or an N-oxide thereof.

In a sixth preferred embodiment the chemical compound of the invention is
represented by Formula VIII (Type 8)



wherein

10 m is 0, 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl,
hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group,
15 which carbocyclic or heterocyclic group optionally may be substituted one or more
times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or
heterocyclic group, which carbocyclic or heterocyclic group optionally may be
20 substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl,
halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl,
25 cycloalkyl, cycloalkyl-alkyl and/or a mono- or polycyclic, carbocyclic or heterocyclic
group, which carbocyclic or heterocyclic groups optionally may be substituted one or
more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
and/or cyano; or

R¹ and R², together with the N atom to which they are bound, form a 5- to
30 7-membered heterocyclic ring.

In a more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro
35 and/or cyano;

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl, or an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or piperidine ring.

In a yet more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

Ar¹ represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R^1 and R^2 , independently of each another, represent hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl, or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

5 R^1 and R^2 , together with the N atom to which they are bound, form a pyrrolidine or piperidine ring.

In a still more preferred embodiment

m is 0 or 1;

n is 0 or 1;

10 X and Y, independently of each another, represent fluoro, CF_3 , nitro and/or cyano;

Ar^1 represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF_3 , nitro and/or cyano;

15 Ar^2 represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF_3 , nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

20 R^1 and R^2 , independently of each another, represent hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl, or 2-oxazolyl, which may be substituted with fluoro, methyl, CF_3 , nitro or cyano; or

R^1 and R^2 , together with the N atom to which they are bound, form a pyrrolidine or piperidine ring.

In a most preferred embodiment the chemical compound of the invention is

25 Tris-(4-fluorophenyl)-methanesulfinic acid amide;

Bis-(4-fluorophenyl)-phenyl-methanesulfinic acid methylamide;

Tris-(4-fluorophenyl)-methanesulfinic acid cyclohexylamide;

1-[Tris-(4-fluorophenyl)-methanesulfinyl]-piperidine;

Tris-(4-fluorophenyl)-methanesulfinic acid dimethylamide;

30 Tris-(4-fluorophenyl)-methanesulfinic acid thiazol-2-ylamide;

Tris-(4-fluorophenyl)-methanesulfinic acid (4-fluorophenyl)-amide;

Bis-(4-fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanesulfinic acid methylamide;

Cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methanesulfinic acid amide;

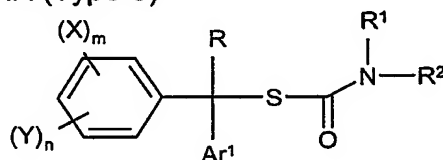
35 Bis-(4-fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanesulfinic acid amide;

Bis-(4-fluorophenyl)-thiazol-2-yl-methanesulfinic acid amide; or

Bis-(4-fluorophenyl)-oxazol-2-yl-methanesulfinic acid amide;

an enantiomer or a mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

In a seventh preferred embodiment the chemical compound of the invention is represented by Formula IX (Type 9)



wherein

m is 0, 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic groups optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R¹ and R², together with the N atom to which they are bound, form a 5- to 7-membered heterocyclic ring.

In a more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-

pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar^2 represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; 5 isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, 10 halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R^1 and R^2 , independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or an aromatic group selected from phenyl; 2, 4 or 5- 15 thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, 20 halogen, haloalkyl, nitro and/or cyano; or

R^1 and R^2 , together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

In a yet more preferred embodiment

m is 0 or 1;

25 n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF_3 , nitro and/or cyano;

Ar^1 represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be 30 substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano;

Ar^2 represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

35 R^1 and R^2 , independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

In a still more preferred embodiment

m is 0 or 1;

5 n is 0 or 1;

X and Y, independently of each another, represent fluoro, CF₃, nitro and/or cyano;

Ar¹ represents phenyl or 2-thiazolyl, which may be substituted once with fluoro, chloro, methyl, CF₃, nitro or cyano;

10 Ar² represents phenyl, which may be substituted once with fluoro, CF₃, nitro or cyano; or

R represents cycloalkyl or cycloalkyl-alkyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl; or

15 R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

In a most preferred embodiment the chemical compound of the invention is

Thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester;

20 Thiocarbamic acid S-[cyclohexyl-bis-(4-fluorophenyl)-methyl] ester;

Thiocarbamic acid S-[cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methyl] ester;

Piperidine-1-carbothioic acid S-[tris-(4-fluorophenyl)-methyl] ester;

Methyl-thiocarbamic acid S-[cyclopentyl-bis-(4-fluorophenyl)-methyl] ester;

25 Pyrrolidine-1-carbothioic acid S-[cyclohexyl-bis-(4-fluorophenyl)-methyl] ester;

Methyl-thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester;

Methyl-thiocarbamic acid S-[cyclopentyl-(2-fluorophenyl)-(4-fluorophenyl)-methyl] ester;

30 Thiocarbamic acid S-[cyclohexyl-(4-fluorophenyl)-pyridin-2-yl-methyl] ester;

Dimethyl-thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester;

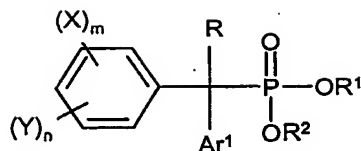
Thiocarbamic acid S-[(2-fluorophenyl)-bis-(4-fluorophenyl)-methyl] ester; or

Thiocarbamic acid S-[(2-fluorophenyl)-(4-fluorophenyl)-phenyl-methyl] ester;

35 an enantiomer or a mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

In an eight preferred embodiment the chemical compound of the invention is represented by Formula X (Type 10)

31



wherein

m is 1 or 2;

n is 0, 1 or 2;

5 X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a phenyl group substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, heterocyclic
10 group other than imidazolyl, which carbocyclic or heterocyclic group may optionally be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

15 R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl; or

R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a 5- to 7-membered heterocyclic ring.

In a more preferred embodiment

20 m is 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

25 Ar¹ represents a phenyl group substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or
30 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R¹ and R², independently of each another, represent alkyl, cycloalkyl or cycloalkyl-alkyl; or

35 R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a 5-to 6-membered heterocyclic ring.

In a yet more preferred embodiment

m is 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro
5 and/or cyano;

Ar¹ represents phenyl, substituted once or twice with fluoro, chloro, CF₃,
nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-
thiazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic group optionally may be
10 substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R¹ and R², independently of each another, represent alkyl, cycloalkyl or
cycloalkyl-alkyl; or

R¹ and R² together with the phosphor and the oxygen atoms to which they
15 are bound form a 5-membered heterocyclic dioxaphospholane ring.

In a still more preferred embodiment

m is 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, CF₃, nitro and/or
20 cyano;

Ar¹ represents phenyl, which is substituted once or twice with fluoro, CF₃,
nitro and/or cyano;

Ar² represents phenyl or 2-thiazolyl, which aromatic group may optionally
be substituted once or twice with fluoro, methyl, CF₃, nitro and/or cyano; or

25 R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and

R¹ and R², independently of each another, represent alkyl or cycloalkyl; or

R¹ and R² together with the phosphor and the oxygen atoms to which they
are bound form a 5-membered heterocyclic dioxaphospholane ring.

In a most preferred embodiment the chemical compound of the invention is

30 [Cyclohexyl-bis-(4-fluorophenyl)-methyl]-phosphonic acid dimethyl ester;

[Cyclopentyl-bis-(4-fluorophenyl)-methyl]-phosphonic acid dipropyl ester;

[1,1-Bis-(4-fluorophenyl)-hexyl]-phosphonic acid dimethyl ester;

[1,1-Bis-(4-fluorophenyl)-2-methyl-propyl]-phosphonic acid dimethyl ester;

[Bis-(4-fluorophenyl)-pyridin-2-yl-methyl]-phosphonic acid dimethyl ester;

35 [Bis-(4-fluorophenyl)-thiazol-2-yl-methyl]-phosphonic acid dimethyl ester;

[Tris-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester;

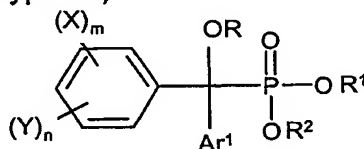
[(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl
ester;

[(2-Chloro-phenyl)-(2-fluoro-phenyl)-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester;

[(4-Chloro-phenyl)-bis-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester;

- 5 [Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methyl]-phosphonic acid; or
[Bis-(4-fluoro-phenyl)-*p*-tolyl-methyl]-phosphonic acid;
an enantiomers or a mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

In a ninth preferred embodiment the chemical compound of the invention is
10 represented by Formula XII (Type 12)



wherein

m is 0, 1 or 2;

n is 0, 1 or 2;

- 15 X and Y, independently of each another, represent alkenyl, alkynyl, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
20 and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

- 25 R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl or alkoxy; or

R¹ and R² together with the phosphor and the oxygen atoms to which they
30 are bound form a heterocyclic (dioxaphospholane) ring.

In a more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, CF₃, nitro
35 and/or cyano;

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl or alkoxy; or

R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a heterocyclic (dioxaphospholane) ring.

In a yet more preferred embodiment

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, CF₃, nitro and/or cyano;

Ar¹ represents phenyl, which may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl or alkoxy; or

R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a heterocyclic (dioxaphospholane) ring.

In a most preferred embodiment the chemical compound of the invention is [Bis-(4-fluorophenyl)-isopropoxy-methyl]-phosphonic acid dimethyl ester;

[(2-Fluorophenyl)-(4-fluorophenyl)-isobutoxy-methyl]-phosphonic acid dimethyl ester;

[(3-Fluorophenyl)-(4-fluorophenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dimethyl ester;

5 2-[Bis-(4-fluorophenyl)-isopropoxy-methyl]-[1,3,2]-dioxaphospholane 2-oxide;

[Cyclohexyl-(4-nitro-3-trifluoromethyl-phenyl)-(pyridin-2-yloxy)-methyl]-phosphonic acid dimethyl ester;

10 [Cyclohexyl-(4-fluorophenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dipropyl ester;

[(4-Chlorophenyl)-(4-fluorophenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dimethyl ester;

[1-(3,4-Dichlorophenoxy)-1-(4-fluorophenyl)-hexyl]-phosphonic acid dimethyl ester;

15 [1-(4-Fluorophenyl)-2-methyl-1-(4-nitro-3-trifluoromethyl-phenoxy)-propyl]-phosphonic acid dimethyl ester;

[(4-Fluorophenyl)-(6-fluoropyridin-2-yloxy)-(4-nitro-3-trifluoromethyl-phenyl)-methyl]-phosphonic acid dimethyl ester;

20 [(3,4-Dichlorophenyl)-(6-fluoropyridin-3-yloxy)-thiazol-2-yl-methyl]-phosphonic acid dimethyl ester; or

[(4-Fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dimethyl ester;

an enantiomer or a mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

25 Any possible combination of two or more of the embodiments described herein is comprised within the scope of the present invention.

Definition of Substituents

30 In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C₁₋₁₈-alkyl), more preferred of from one to six carbon atoms (C₁₋₆-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, 35 tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C₁₋₄-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C₁₋₃-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a haloalkyl group designates an alkyl group as defined herein, which alkyl group is substituted one or more times with halogen. Preferred haloalkyl groups of the invention include trihalogenmethyl.

In the context of this invention a hydroxy-alkyl group designates an alkyl
5 group substituted with OH, wherein alkyl is as defined above.

In the context of this invention a cyano-alkyl group designates an alkyl group substituted with CN, wherein alkyl is as defined above.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a
10 preferred embodiment the alkenyl group of the invention comprises of from two to eight carbon atoms (C₂₋₈-alkenyl), more preferred of from two to six carbon atoms (C₂₋₆-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl; 1-, 2- or 3-butenyl, 1,3-butadienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexadienyl, or 1,3,5-hexatrienyl; 1-, 2-, 3-, 4-,
15 5-, 6-, or 7-octenyl, 1,3-octadienyl, 1,3,5-octatrienyl, or 1,3,5,7-octetraenyl.

In the context of this invention a haloalkenyl group designates an alkenyl group as defined herein, which alkenyl group is substituted one or more times with halogen.

In the context of this invention an alkynyl group designates a carbon chain
20 containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to eight carbon atoms (C₂₋₈-alkynyl), more preferred of from two to six carbon atoms (C₂₋₆-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, 1,3-butadiynyl; 1-, 2-, 3-, 4-pentynyl, 1,3-pentadiynyl; 1-, 2-, 3-, 4-, or 5-hexynyl, 1,3-hexadiynyl, 1,3,5-hexatriynyl; 1-, 2-, 3-, 4-, 5- or 6-heptynyl, 1,3-heptadiynyl, 1,3,5-heptatriynyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-octynyl, 1,3-octadiynyl, 1,3,5-octatriynyl, or 1,3,5,7-octetraynyl.

In the context of this invention a haloalkynyl group designates an alkynyl
30 group as defined herein, which alkynyl group is substituted one or more times with halogen.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C₃₋₇-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

35 In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, and an alkoxy-alkoxy-alkyl group designates an "alkyl-O-alkyl-O-alkyl-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkyl groups of the invention include methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl, and examples of preferred alkoxy-alkoxy-alkyl groups of the invention include methoxy-methoxy-methyl, methoxy-methoxy-ethyl, methoxy-ethoxy-methyl, and methoxy-ethoxy-ethyl.

In the context of this invention an alkoxy-alkoxy group designates an "alkyl-O-alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkoxy groups of the invention include methoxy-methoxy, methoxy-ethoxy, ethoxy-methoxy, and ethoxy-ethoxy.

In the context of this invention an alkoxy-alkoxy-alkyl group designates an "alkyl-O-alkyl-O-alkyl-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkoxy groups of the invention include methoxy-methoxy-methyl, methoxy-ethoxy-methyl, ethoxy-methoxy-methyl, ethoxy-ethoxy-methyl, methoxy-methoxy-ethyl, methoxy-ethoxy-ethyl, ethoxy-methoxy-ethyl, and ethoxy-ethoxy-ethyl.

In the context of this invention an acyl group designates a carboxy group (-COOH) or an alkyl-carbonyl group (alkyl-CO-), wherein alkyl is as defined above. Examples of preferred acyl groups of the invention include carboxy, acetyl, and propionyl.

In the context of this invention an alkoxy-carbonyl group designates an "alkyl-O-CO-" group, and an alkoxy-alkoxy-carbonyl group designates an "alkyl-O-alkyl-O-CO-" group, wherein alkyl is as defined above.

In the context of this invention an amino group may be a primary (-NH₂), secondary (-NH-alkyl), or tertiary (-N(alkyl)₂) amino group, i.e. it may be substituted once or twice with an alkyl group as defined above.

In the context of this invention a mono-, bi- or polycyclic carbocyclic group is a mono-, bi- or polycyclic compound, which holds only carbon atoms in its ring structure. The ring structures may in particular be aromatic (i.e. aryl) or partially or fully saturated.

In the context of this invention an aryl group designates a monocyclic or polycyclic aromatic hydrocarbon group. Examples of preferred aryl groups of the invention include phenyl, indenyl, naphthyl, azulenyl, fluorenyl, and anthracenyl.

In the context of this invention an aralkyl group designates an aryl group as defined above, which aryl group is attached to an alkyl group as also defined above. Examples of preferred aralkyl groups of the invention include benzyl.

In the context of this invention a mono-, bi- or polycyclic heterocyclic group is a mono-, bi- or polycyclic compound, which holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). One or more of the ring structures may in particular be aromatic or partially saturated (i.e. a heteroaryl), or fully saturated.

Preferred monocyclic heteroaryl groups of the invention include aromatic 5- and 6 membered heterocyclic monocyclic groups, including furanyl, in particular 2- or 3-furanyl; thienyl, in particular 2 or 3-thienyl; pyrrolyl (azolyl), in particular 1,2 or 3-pyrrolyl; oxazolyl, in particular oxazol-2,4 or 5-yl; thiazolyl, in particular thiazol-2,4 or 5-yl; imidazolyl, in particular 1,2 or 4-imidazolyl; pyrazolyl, in particular 1,3 or 4-pyrazolyl; isoxazolyl, in particular isoxazol-3,4 or 5-yl; isothiazolyl, in particular isothiazol-3,4 or 5-yl; oxadiazolyl, in particular 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4-oxadiazol-3,4 or 5-yl; triazolyl, in particular 1,2,3-, 1,2,4-, 2,1,3- or 4,1,2-triazolyl; thiadiazolyl, in particular thiadiazol-3,4 or 5-yl; pyridinyl, in particular 2,3 or 4-pyridinyl; pyridazinyl, in particular 3 or 4-pyridazinyl; pyrimidinyl, in particular 2,4 or 5-pyrimidinyl; pyrazinyl, in particular 2 or 3-pyrazinyl; and triazinyl, in particular 1,2,3-, 1,2,4- or 1,3,5-triazinyl.

Preferred bicyclic heteroaryl groups of the invention include indoliziny, in particular 2,5 or 6-indoliziny; indolyl, in particular 2,5 or 6-indolyl; isoindolyl, in particular 2,5 or 6-isoindolyl; benzo[b]furanyl, in particular 2,5 or 6-benzofuranyl; benzo[b]thienyl, in particular 2,5 or 6-benzothienyl; benzimidazolyl, in particular 2,5 or 6-benzimidazolyl; benzothiazolyl, in particular 5 or 6-benzothiazolyl; purinyl, in particular 2 or 8-purinyl; quinolinyl, in particular 2,3,6 or 7-quinolinyl; isoquinolinyl, in particular 3,6 or 7-isoquinolinyl; cinnolinyl, in particular 6 or 7-cinnolinyl; phthalazinyl, in particular 6 or 7-phthalazinyl; quinazolinyl, in particular 2,6 or 7-quinazolinyl; quinoxalinyl, in particular 2 or 6-quinoxalinyl; 1,8-naphthyridinyl, in particular 1,8-naphthyridin-2,3,6 or 7-yl; pteridinyl, in particular 2,6 or 7-pteridinyl; and indenyl, in particular 1,2,3,5 or 5-indenyl.

In the context of this invention a heteroaryl-alkyl group designates a mono-, bi- or poly-heterocyclic group as described above, which heterocyclic group is attached to an alkyl group as also defined above. Examples of preferred hetero-alkyl groups of the invention include furfuryl and picolyl.

In the context of this invention an N-oxide designates an oxide derivative of a nitrogen containing compound, e.g. N-containing heterocyclic compounds capable of forming such N-oxides.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e.

physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

Steric Isomers

The chemical compounds of the invention may exist in (+) and (-) forms as well as in racemic forms (\pm). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

The chemical compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from
5 commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation,
10 chromatography, etc.

Biological Activity

According to the present invention it has now been found that the chemical compounds of the invention possess valuable activity as modulators of SK_{Ca} and/or
15 IK_{Ca} channels, in particular by having an inhibitory activity.

The SK/IK/BK channel modulating or inhibiting activity may be monitored using conventional electrophysiological methods such as patch-clamp techniques, or conventional spectroscopic methods such as FLIPR assay (Fluorescence Image Plate Reader; available from Molecular Devices). These methods generally comprises
20 subjecting an SK_{Ca} and/or IK_{Ca} containing cell to the action of the chemical compound of the invention, followed by monitoring the membrane potential of the SK_{Ca} and/or IK_{Ca} containing cell in order to identify changes in the membrane potential caused by the action of the compound of the invention. Using such methods the chemical compounds of the invention show IK_{Ca} inhibitory activity in concentrations below 100
25 μ M, preferably below 10 μ M, more preferred below 1 μ M. In its most preferred embodiment compounds show IK_{Ca} inhibitory activity show activity in low micromolar and the nanomolar range.

Based on their biological activity the compounds of the invention are considered useful for the for the treatment, prevention or alleviation of a disease or a
30 disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of SK_{Ca} and/or IK_{Ca} channels, including diseases or conditions like respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms,
35 urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent

claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

The compounds of the invention are considered particularly useful for
5 reducing or inhibiting undesired immune-regulatory actions. In a preferred embodiment, therefore, the compounds of the may be used in the treatment or alleviation of a diseases, disorders or condition related to immune dysfunction, or in order to obtain immune suppression in an individual in need therefore.

In a more preferred embodiment, the invention relates to the use of an IK_{Ca}
10 inhibitory compound of the invention in a combination therapy with known immune-suppressants for the treatment or alleviation of a diseases, disorders or condition related to immune dysfunction, or for obtaining immune suppression. Preferred immune-suppressants to combine with the compounds of the invention include Amphotericin, Busulphan, Co-trimoxazole, Chlorambucil, colony stimulating factors,
15 corticosteroids, Cyclophosphamide, Fluconazole, folinic acid, Ganciclovir, antilymphocyte immunoglobulins, normal immunoglobulins, Methotrexate, Methylprednisolone, Octreotide, Oxpentifylline, Tacrolimus (FK506), Thalidomide, Zolimomab aritox, and the calcineurin inhibitors (protein phosphatase 2B inhibitors), in particular Cyclosporin.

20 Conditions which may benefit from this treatment include, but are not limited to diseases, disorders or conditions such as auto-immune diseases, e.g. Addison's disease, alopecia areata, Ankylosing spondylitis, haemolytic anemia (anemia haemolytica), pernicious anemia (anemia perniciosa), aphthae, aphthous stomatitis, arthritis, arteriosclerotic disorders, osteoarthritis, rheumatoid arthritis,
25 aspermiogenese, asthma bronchiale, auto-immune asthma, auto-immune hemolysis, Bechet's disease, Boeck's disease, inflammatory bowel disease, Burkitt's lymphoma, Chron's disease, chorioiditis, colitis ulcerosa, Coeliac disease, cryoglobulinemia, dermatitis herpetiformis, dermatomyositis, insulin-dependent type I diabetes, juvenile diabetes, idiopathic diabetes insipidus, insulin-dependent diabetes mellisis, auto-
30 immune demyelinating diseases, Dupuytren's contracture, encephalomyelitis, encephalomyelitis allergica, endophthalmia phacoanaphylactica, enteritis allergica, auto-immune enteropathy syndrome, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, glomerulo nephritis, Goodpasture's syndrome, Graves' disease, Hamman-Rich's disease, Hashimoto's
35 disease, Hashimoto's thyroiditis, sudden hearing loss, sensoneural hearing loss, hepatitis chronica, Hodgkin's disease, haemoglobinuria paroxysmatica, hypogonadism, ileitis regionalis, iritis, leucopenia, leucemia, lupus erythematosus disseminatus, systemic lupus erythematosus, cutaneous lupus erythematosus, lymphogranuloma malignum, mononucleosis infectiosa, myasthenia gravis, traverse

myelitis, primary idiopathic myxedema, nephrosis, ophthalmia sympathica, orchitis granulomatosa, pancreatitis, pemphigus, pemphigus vulgaris, polyarteritis nodosa, polyarthritis chronica primaria, polymyositis, polyradiculitis acuta, psoriasis, purpura, pyoderma gangrenosum, Quervain's thyroiditis, Reiter's syndrome, sarcoidosis, ataxic sclerosis, progressive systemic sclerosis, scleritis, sclerodermia, multiple sclerosis, sclerosis disseminata, acquired spenic atrophy, infertility due to antispermatozoan antibodies, thrombocytopenia, idiopathic thrombocytopenia purpura, thymoma, acute anterior uveitis, vitiligo, AIDS, HIV, SCID and Epstein Barr virus associated diseases such as Sjorgren's syndrome, virus (AIDS or EBV) associated B cell lymphoma, parasitic diseases such as Lesihmania, and immunosuppressed disease states such as viral infections following allograft transplantations, graft vs. Host syndrome, transplant rejection, or AIDS, cancers, chronic active hepatitis diabetes, toxic chock syndrome, food poisoning, and transplant rejection.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to inhibition of SK_{Ca} and/or IK_{Ca} channels, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a chemical compound of the invention.

In a more preferred embodiment the disease or a disorder or a condition is a respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophla, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

In an even more preferred embodiment, the disease, disorder or condition relates to reduction or inhibition of undesired immune-regulatory actions, including

graft vs. host syndrome, transplant rejection, or transplant rejection. In a further preferred embodiment this method comprises simultaneous administration of a pharmaceutically effective amount of a conventional immune suppressing agent. Conventional immune-suppressing agent for use according to the invention include

- 5 Amphotericin, Busulphan, Co-trimoxazole, Chlorambucil, colony stimulating factors, corticosteroids, Cyclophosphamide, Fluconazole, folinic acid, Ganciclovir, antilymphocyte immunoglobulins, normal immunoglobulins, Methotrexate, Methylprednisolone, Octreotide, Oxpentifylline, Tacrolimus (FK506), Thalidomide, Zolimomab aritox, or the calcineurin inhibitors (protein phosphatase 2B inhibitors), in
10 particular Cyclosporin.

- Conditions which may benefit from this treatment include, but are not limited to diseases, disorders or conditions such as auto-immune diseases, e.g. Addison's disease, alopecia areata, Ankylosing spondylitis, haemolytic anemia (anemia haemolytica), pernicious anemia (anemia perniciosa), aphthae, aphthous
15 stomatitis, arthritis, arteriosclerotic disorders, osteoarthritis, rheumatoid arthritis, aspermiogenese, asthma bronchiale, auto-immune asthma, auto-immune hemolysis, Bechet's disease, Boeck's disease, inflammatory bowel disease, Burkitt's lymphoma, Chron's disease, chorioiditis, colitis ulcerosa, Coeliac disease, cryoglobulinemia, dermatitis herpetiformis, dermatomyositis, insulin-dependent type I diabetes, juvenile
20 diabetes, idiopathic diabetes insipidus, insulin-dependent diabetes mellisis, auto-immune demyelinating diseases, Dupuytren's contracture, encephalomyelitis, encephalomyelitis allergica, endophthalmia phacoanaphylactica, enteritis allergica, auto-immune enteropathy syndrome, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, glomerulo nephritis,
25 Goodpasture's syndrome, Graves' disease, Hamman-Rich's disease, Hashimoto's disease, Hashimoto's thyroiditis, sudden hearing loss, sensoneural hearing loss, hepatitis chronica, Hodgkin's disease, haemoglobinuria paroxysmatica, hypogonadism, ileitis regionalis, iritis, leucopenia, leucemia, lupus erythematosus disseminatus, systemic lupus erythematosus, cutaneous lupus erythematosus,
30 lymphogranuloma malignum, mononucleosis infectiosa, myasthenia gravis, traverse myelitis, primary idiopathic myxedema, nephrosis, ophthalmia symphatica, orchitis granulomatosa, pancreatitis, pemphigus, pemphigus vulgaris, polyarteritis nodosa, polyarthritis chronica primaria, polymyositis, polyradiculitis acuta, psoriasis, purpura, pyoderma gangrenosum, Quervain's thyreoiditis, Reiter's syndrome, sarcoidosis,
35 ataxic sclerosis, progressive systemic sclerosis, scleritis, sclerodermia, multiple sclerosis, sclerosis disseminata, acquired spenic atrophy, infertility due to antispermatozoan antibodies, thrombocytopenia, idiopathic thrombocytopenia purpura, thymoma, acute anterior uveitis, vitiligo, AIDS, HIV, SCID and Epstein Barr virus associated diseases such as Sjorgren's syndrome, virus (AIDS or EBV)

associated B cell lymphoma, parasitic diseases such as Leishmania, and immunosuppressed disease states such as viral infections following allograft transplantations, graft vs. Host syndrome, transplant rejection, or AIDS, cancers, chronic active hepatitis diabetes, toxic shock syndrome, food poisoning, and
5 transplant rejection.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon
10 the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

15

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed. These examples demonstrate general methods for the synthesis of the preferred compounds in this invention, and some preferred methods for synthesis of
20 certain embodied compounds.

2-[Bis-(4-fluoro-phenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-thiazole (Compound 1)

A solution of thiazole (2.6 g) in THF (20 ml) at -78°C under nitrogen was
25 treated with 2.5M *n*-BuLi (12.25 ml) over 15 min. After stirring for 30 min a solution of *p*-fluorobenzophenone (6.54 g) in THF (20 ml) was added and stirring continued overnight with gradual warming to room temperature. The reaction was quenched with sat. aq. NH₄Cl and extracted with ethyl ether (3x). Drying (MgSO₄), filtration and concentration afforded the carbinol as a solid (8.5 g, m.p. = 88.6-89.5°C). This
30 material (0.5 g) was dissolved in DMF (5 ml) and treated with NaH (60% dispersion in paraffin, 76 mg). After stirring for 45 min at room temperature 5-fluoro-2-nitrobenzotrifluoride (0.44 g) was added and the reaction heated to 60°C. After 5 days the reaction was quenched with sat. aq. NH₄Cl and extracted with ethyl ether (3x). Drying of the combined organic layers (MgSO₄), filtration, concentration and flash
35 chromatography afforded the title compound (9%; M.p. 133-134°C).

2-[2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methoxy]-[1,3,2]-dioxaphospholane (Compound 2)

o-Fluorophenyl-di-*p*-fluorophenylmethanol (628 mg) dissolved in dry toluene
40 (10 ml) was treated with 2-chloro-1,3,2-dioxaphospholane (292 mg) and refluxed for

10 hrs. The toluene was evaporated and the crude residue was purified by flash column chromatography to afford 260 mg of the title compound (32%; M.p. 163-164°C).

2-[Tris-(4-fluoro-phenyl)-methoxy]-[1,3,2]-dioxaphospholane (Compound 3)

5 was prepared in similar fashion in 14% yield, m.p. 195-196°C.

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-enenitrile (Compound 4)

o-Fluorophenyl-*p*-fluorophenylacetonitrile (1.0 g) was dissolved in dry DME (5 ml) and treated with NaH (60% dispersion in paraffin, 190 mg). After stirring for 30-10 45 min. at room temperature allyl bromide (0.8 g) was added and stirring continued overnight. The reaction was quenched with sat. aq. NH₄Cl and extracted with ethyl acetate (3x). Drying of the combined organic layers (MgSO₄), filtration, concentration and flash chromatography afforded the title compound (39%; M.p. 215-219°C).

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3-methyl-butyronitrile (Compound 5)

15 was prepared in similar fashion in 47% yield, isolated as an oil.

2,2-Bis-(4-fluoro-phenyl)-3-methyl-butyronitrile (Compound 6) was prepared in similar fashion in 52% yield, isolated as an oil.

2,2-Bis-(4-fluoro-phenyl)-4-methyl-pentanenitrile (Compound 7) was prepared in similar fashion in 65% yield, isolated as an oil.

20 2,2-Bis-(4-fluoro-phenyl)-pent-4-enenitrile (Compound 8) was prepared in similar fashion in 70% yield, isolated as an oil.

2,2-Bis-(4-fluoro-phenyl)-pent-4-ynenitrile (Compound 9) was prepared in similar fashion in 62% yield, m.p. 59.7-60.5°C.

25 2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-ynenitrile (Compound 10) was prepared in similar fashion in 33% yield, isolated as an oil.

2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-4-methyl-pentanenitrile (Compound 11) was prepared in similar fashion in 79% yield, isolated as an oil.

2,2-Bis-(4-fluoro-phenyl)-3,3-diphenyl-propionitrile (Compound 12) was prepared in similar fashion in 84% yield, m.p. 208-212.5°C.

30 2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3,3-diphenyl-propionitrile (Compound 13) was prepared in similar fashion in 76% yield, m.p. 210-215.3°C.

2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3-methyl-butyronitrile (Compound 14) was prepared in similar fashion in 65% yield, isolated as an oil.

35 2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-4-methyl-pentanenitrile (Compound 15) was prepared in similar fashion in 51% yield, isolated as an oil.

2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-enenitrile (Compound 16) was prepared in similar fashion in 72% yield, isolated as an oil.

2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-ynenitrile (Compound 17) was prepared in similar fashion in 73% yield, isolated as an oil.

2,2-Bis-(4-fluoro-phenyl)-3-oxo-butyronitrile (Compound 18) was prepared in similar fashion in 38% yield, m.p. < 50°C.

2,2-Bis-(4-fluoro-phenyl)-3-methyl-butyramide (Compound 19)

5 2,2-Bis-(4-fluoro-phenyl)-3-methyl-butyronitrile (2.21 g) was suspended in acetic acid (2 ml) and conc. sulphuric acid (2 ml) and heated to 130°C for 1.5 hrs. The reaction mixture was poured onto ice/water and the pH adjusted to 9 with aq. ammonium hydroxide. The mixture was extracted with dichloromethane (3x), washed with water (2x) and brine, dried (MgSO₄), filtered and concentrated. The product was
10 taken up in dichloromethane and triturated with cold hexane to precipitate the title compound (50%; M.p. 142.3-147.0°C).

3-Ethoxy-2-(4-fluoro-phenyl)-2-(2-fluoro-phenyl)-propionitrile (Compound 20)

A solution of *o*-fluorophenyl-*p*-fluorophenylacetonitrile (1.7 g) in THF (10 ml)
15 was treated with sodium hydride (60% dispersion in paraffin) (0.2 g) under Argon. To the formed suspension, chloromethyl ethyl ether (0.8 g) was added dropwise and the reaction mixture was stirred at room temperature overnight. The mixture was filtered and concentrated. Flash chromatography of the residue afforded the title compound (1.1 g; Isolated as an oil).

20 3-Ethoxy-2,2-bis-(4-fluoro-phenyl)-propionitrile (Compound 21) was prepared in similar fashion in 80% yield from di-*p*-fluorophenylacetonitrile and chloromethyl ethyl ether, isolated as an oil.

Cyano-(4-fluoro-phenyl)-(2-fluoro-phenyl)-acetic acid methyl ester (Compound 22) was prepared in similar fashion in 23% yield from *o*-fluorophenyl-*p*-
25 fluorophenylacetonitrile and methyl chloroformate, m.p. 104-105°C.

2,2-Bis-(4-fluoro-phenyl)-3-(2-methoxy-ethoxy)-propionitrile (Compound 23) was prepared in similar fashion in 70% yield from di-*p*-fluorophenylacetonitrile and MEM-chloride, isolated as an oil.

2,2-Bis-(4-fluoro-phenyl)-succinonitrile (Compound 24) was prepared in
30 similar fashion in 38% yield from di-*p*-fluorophenylacetonitrile and chloroacetonitrile, m.p. 93-94°C.

3-Cyano-3-(4-fluoro-phenyl)-3-(2-fluoro-phenyl)-propionic acid ethyl ester (Compound 25)

35 A solution of *o*-fluorophenyl-*p*-fluorophenylacetonitrile (1.7 g) in ethylmethyl ketone (10 ml) was treated with potassium carbonate (2 g) and potassium iodide (0.1 g). To the formed suspension, ethyl bromoacetate (2 g) was added dropwise and the reaction mixture was refluxed overnight. The mixture was filtered and concentrated. Flash chromatography of the residue afforded the title compound (1.4 g; Viscous
40 gum).

3-Cyano-3,3-bis-(4-fluoro-phenyl)-propionic acid ethyl ester (Compound 26)

was prepared in similar fashion in 61% yield using di-*p*-fluorophenylacetonitrile and ethyl bromoacetate, isolated as an oil.

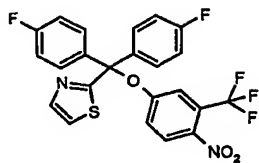
5 2-[Cyano-bis-(4-fluoro-phenyl)-methyl]-malonic acid diethyl ester (Compound 27)

To THF (80 ml) were added sequentially, a 1.0 M solution of TiCl_4 in dichloromethane (80 ml), *p,p'*-difluorobenzophenone (8.73 g) and diethyl malonate (6.4 g) in THF 20 ml. After stirring at 0°C for 40 min, a solution of pyridine (12.8 ml) in THF (28 ml) was added dropwise. The ensuing mixture was stirred for 4 days. The
10 reaction was quenched with water and diethyl ether. The aqueous phase was separated and extracted twice more with diethyl ether. The combined organic phases were washed with brine, sat. sodium bicarbonate solution and again with brine. Drying of the organic phase (MgSO_4), filtration and concentration afforded a residue from which residual diethyl malonate was removed by *Kugelrohr* distillation. The residue
15 was flash chromatographed to provide 1,1-di-*p*-fluorophenyl-2,2-diethoxycarbonylethylene (25%, m.p. = 117 – 119°C). To this product (5.9 g) were added ammonium chloride (1.31 g), KCN (2.18 g), DMF (175 ml) and water (22 ml) and the mixture was heated to 100°C for 8 hrs. The cooled reaction mixture was poured into water and extracted (3x) with ethyl ether. The combined organic phases
20 were washed with water, aq. 2N HCl, aq. 5% NaHCO_3 and brine. Drying (Na_2SO_4), filtration and evaporation of volatiles gave a residue which was recrystallised from ether-hexane to afford the title compound (56%; M.p. 90-91°C).

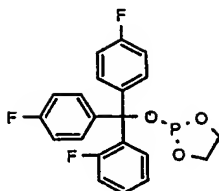
2,2-Bis-(4-fluoro-phenyl)-4-hydroxy-butyronitrile (Compound 28)

25 Ethylene glycol dimethyl ether (10 ml) was treated with sodium borohydride (142 mg) and LiCl (228 mg) and the mixture stirred for 30 min. 3-Cyano-3,3-bis-(4-fluoro-phenyl)-propionic acid ethyl ester (847 mg) was added and the mixture stirred for 6 hrs, before more sodium borohydride (36 mg) and LiCl (57 mg) were added and stirring continued overnight. The mixture was poured into water and extracted (3x) with
30 ethyl ether. The combined organic extracts were dried over Na_2SO_4 . Filtration, concentration and flash chromatography of the residue afforded the title compound (41%; Isolated as an oil).

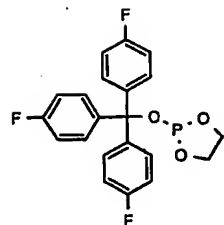
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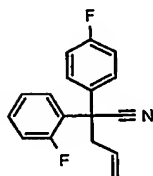
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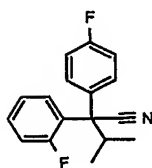
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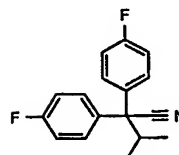
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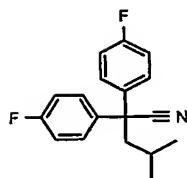
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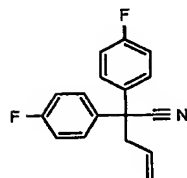
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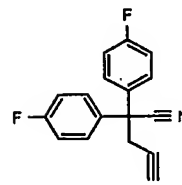
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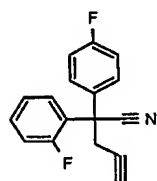
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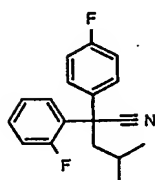
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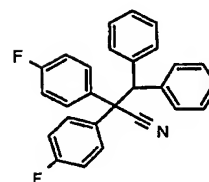
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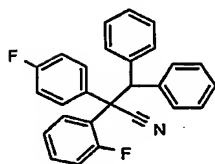
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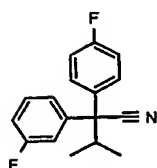
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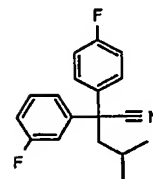
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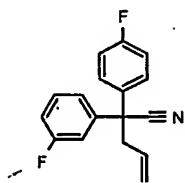


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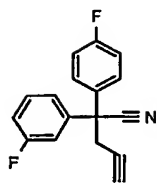


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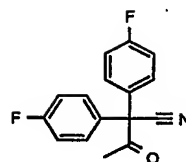
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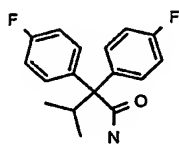
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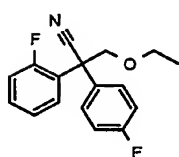
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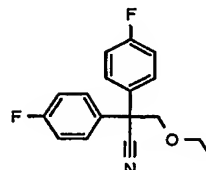
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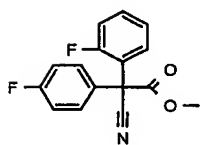
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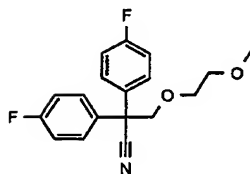
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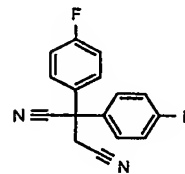
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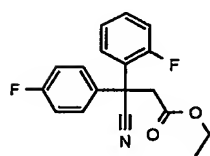
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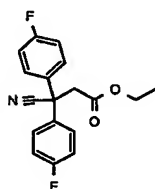
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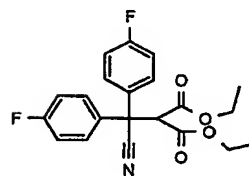
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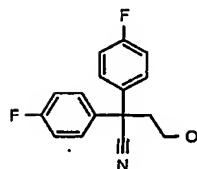
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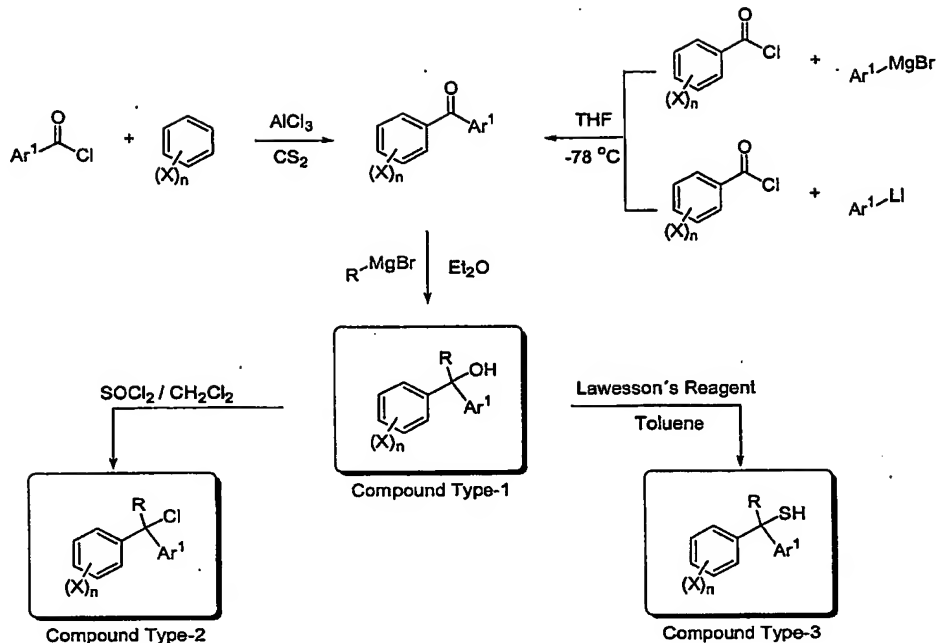
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General method for the preparation of compound Type 1

Synthesis of tri substituted methanole:

- 5 A solution of a substituted benzene (2,5 equivalent) and aluminum chloride (5 equivalent) in dry carbon disulfide (0.5 L/mol) is heated to gentle reflux. An arylcarbonylchloride (2 equivalent) is added slowly from a dropping funnel. After 1 hour the addition is completed and the gentle reflux is continued for another hour. The dropping funnel is removed, a condenser is attached and carbon disulfide is distilled.
- 10 The reaction mixture is poured slowly over a mixture of cracked ice and hydrochloric acid. The aqueous phase is extracted twice with toluene, the extract are combined and washed with water, aqueous sodium hydroxide and dried over sodium sulfate. Evaporation of the solvent gave the phenyl-aryl ketone in 69-90% yield.

- The substituted phenyl-aryl ketone is added drop-wise to a refluxing
- 15 solution of a Grignard Reagents in ether. After 3 hours the reaction mixture is cooled and poured into water. The aqueous phase is extracted twice with methylene chloride and the combined organic phases is dried with sodium sulfate, filtrated and the solvent evaporated. The crude product are crystallized or purified by column chromatography to give trisubstitutedmethanoles in 73-90% yield.

20

General method for the preparation of compound Type 2

Synthesis of tri substituted chloromethane:

A solution of a compound Type 1 in methylene chloride (2 mL/mmol) is heated to gentle reflux. Thionylchloride (2 equivalent) is added from a dropping funnel

during 15 minutes and the reflux is continued for another 1 hour. Excess thionylchloride and methylene chloride is removed by evaporation. Toluene is added twice, and evaporated to afford crude tri substituted chloromethane in 95-100% yield. This product was used without purification in the next step.

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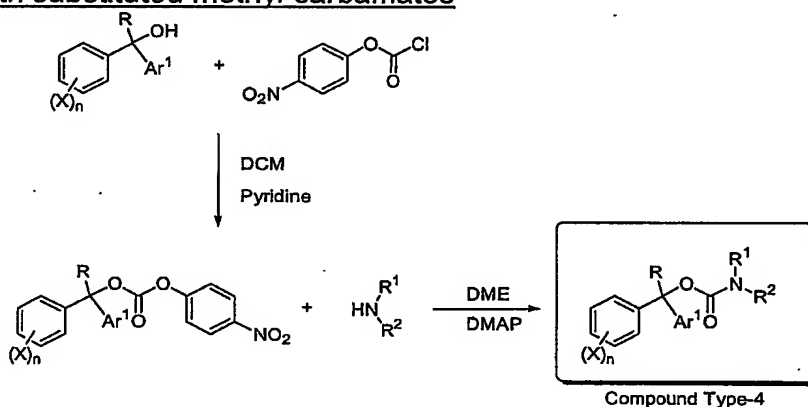
General method for the preparation of compound Type 3

Synthesis of tri substituted methyl mercaptane:

A solution of a compound Type 1 in toluene is heated to gentle reflux with 2,4-bis(p-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulphide for 1 hour. Toluene is removed by evaporation and the crude product is purified by column chromatography affording tri substituted methyl mercaptane in 90-100% yield.

General method for the preparation of compound Type 4

Synthesis of tri substituted methyl carbamates



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A compound Type 1 is dissolved in dichloromethane (DCM) (3 mL/mmol), pyridine (1 equivalent) and 4-nitrophenyl chloroformate (1 equivalent) are added and the solution is heated to reflux for 3 hour. The reaction mixture is cooled washed with aq hydrochloric acid, 10% sodium carbonate and water. Dried with magnesium sulfate, filtrated and the solvent removed under reduced pressure. The crude product is purified by column chromatography affording substituted carbonate in 77-86% yield.

The substituted carbonate is dissolved in dimethoxyethane (DME) (3 mL/mmol), and the amine is added (1 equivalent) together with 4-dimethylaminopyridine (DMAP) (1 equivalent). The reaction mixture is heated for 14 hours at 50°C, cooled to room temperature, washed with aq hydrochloric acid, 10% sodium carbonate and water. Dried with magnesium sulfate, filtrated and the solvent removed under reduced pressure. The crude product is purified by column chromatography affording substituted carbamate in 74-80% yield.

In this way the following tri substituted methyl carbamates are obtained:

(±)-Carbamic acid tris-(4-fluorophenyl)-methyl ester (Compound 4-1);

30

(±)-Carbamic acid cyclohexyl-bis-(4-fluorophenyl)-methyl ester (Compound 4-2);

(±)-Carbamic acid cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methyl ester (Compound 4-3);

5 (±)-Piperidine-1-carboxylic acid tris-(4-fluorophenyl)-thiazol-2-yl-methyl ester (Compound 4-4);

(±)-Methyl-carbamic acid cyclopentyl-bis-(4-fluorophenyl)-methyl ester (Compound 4-5);

10 (±)-Pyrrolidine-1-carboxylic acid cyclohexyl-bis-(4-fluorophenyl)-methyl ester (Compound 4-6);

(±)-Methyl-carbamic acid tris-(4-fluorophenyl)-methyl ester (Compound 4-7);

(±)-Methyl-carbamic acid cyclohexyl-(2-fluorophenyl)-(4-fluorophenyl)-methyl ester (Compound 4-8);

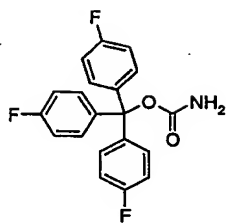
15 (±)-Carbamic acid cyclohexyl-(4-fluorophenyl)-pyridin-2-yl-methyl ester (Compound 4-9);

(±)-Dimethyl-carbamic acid tris-(4-fluorophenyl)-methyl ester (Compound 4-10);

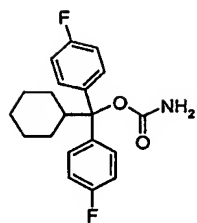
(±)-Carbamic acid (2-fluorophenyl)-bis-(4-fluorophenyl)-methyl ester (Compound 4-11); and

20 (±)-Carbamic acid (2-fluorophenyl)-(4-fluorophenyl)-phenyl-methyl ester (Compound 4-12).

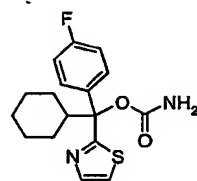
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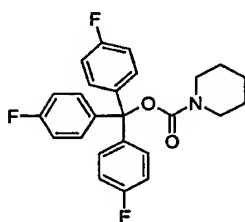
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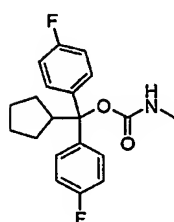
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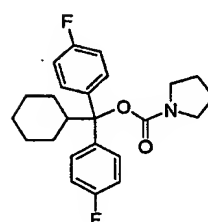
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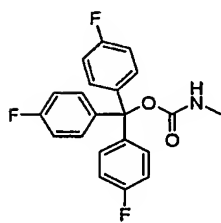
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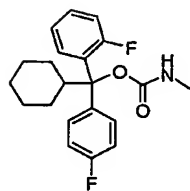
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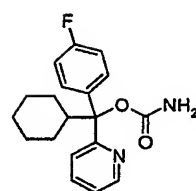
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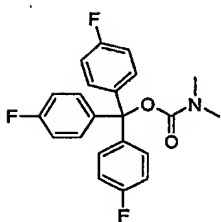
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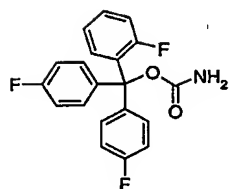
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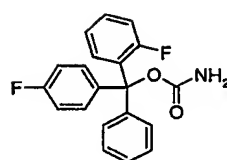
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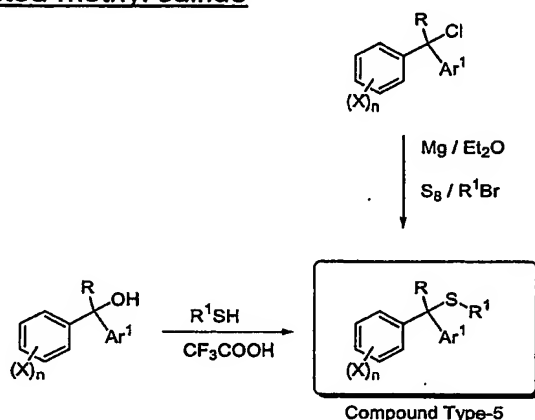
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4-11



4-12

General method for the preparation of compound Type 5Synthesis of tri substituted methyl sulfide

Magnesium turnings in anhydrous diethyl ether is heated to gentle reflux,
 5 and a solution of compound Type 2 (1 equivalent) in anhydrous diethyl ether is added slowly from a dropping funnel at such a rate that gentle reflux continue without further heating. When the addition is completed, the reaction mixture is heated to gentle reflux until only traces of unreacted magnesium remains. The reaction mixture is cooled in an ice bath, and finely powdered sulfur (1 equivalent) is added and the
 10 reaction is heated to gentle reflux for another 1 hour. (OBS! A vigorous reaction with sulfur takes place when the reaction is heated for reflux).

The reaction mixture is cooled again on the ice bath, alkyl bromide (1.1 equivalent) is added dropwise from the funnel, and the mixture is heated for reflux 16 hours then cooled. DCM is added and the reaction mixture is washed twice with 5%
 15 sodium hydroxide and twice with water. Dried with magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (hexane:DCM) affording sulfide Type 5 in 60-84% yield.

In this way the following tri substituted methyl sulfides are obtained:

- 20 2-[Cyclohexyl-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfanyl]-thiazole (Compound 5-1);
 2-[(2-Chlorophenyl)-cyclohexyl-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfanyl]-1-methyl-1*H*-imidazole (Compound 5-2);
 2-[(4-Chlorophenylsulfanyl)-cyclopentyl-(4-fluorophenyl)-(2-fluorophenyl)-methyl]-pyridine (Compound 5-3);
 25 2-[Cyclohexyl-(3,4-dichlorophenyl)-(1*H*-imidazol-2-yl)-methylsulfanyl]-pyridine (Compound 5-4);
 2-[Cyclopentyl-(2-fluorothiazol-4-yl)-(4-nitro-3-trifluoromethylphenyl)-methylsulfanyl]-pyridine (Compound 5-5);
 30 2-[(4-fluorophenyl)-(4-fluorophenylsulfanyl)-(4-nitro-3-trifluoromethylphenyl)-methyl]-thiazole (Compound 5-6);

2-[Cyclohexylsulfanyl-(4-fluorophenyl)-(4-nitro-3-trifluoromethylphenyl)-methyl]-thiazole (Compound 5-7);

2-[Cyclopentylsulfanyl-bis-(4-fluorophenyl)-methyl]-1-methyl-1*H*-imidazole (Compound 5-8);

5 4-[Cyclohexylsulfanyl-bis-(4-fluorophenyl)-methyl]-2-fluoro-thiazole (Compound 5-9);

2-[Bis-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfonyl]-thiazole (Compound 5-10);

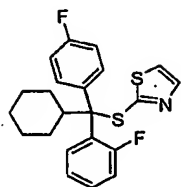
1-Methyl-2-[tris-(4-fluorophenyl)-methylsulfanyl]-1*H*-imidazole (Compound 10 5-11); Mp. 135.5-140.5°C;

2-[Tris-(4-fluorophenyl)-methylsulfanyl]-pyridine (Compound 5-12); isolated as an oil; and

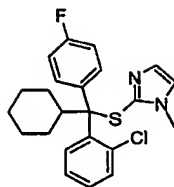
2-[Tris-(4-fluorophenyl)-methylsulfanyl]-pyridine-N-oxide (Compound 5-13); Mp. 147.7-151.8°C.

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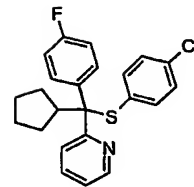
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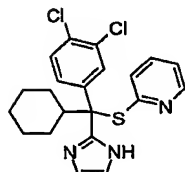
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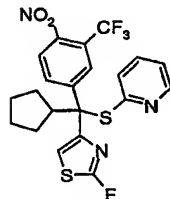
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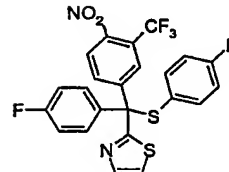
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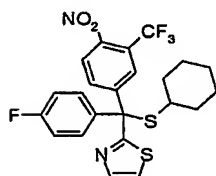
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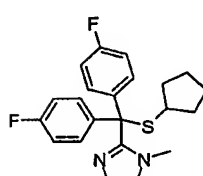
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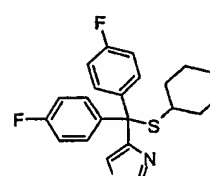
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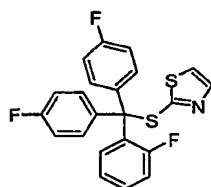
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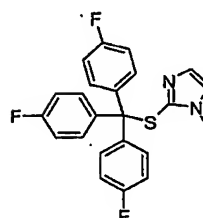
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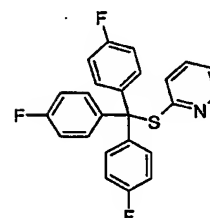
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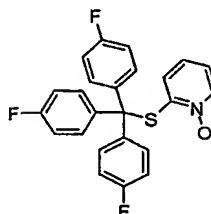
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5-12



5-13

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-N,N-diethyl-acetamide
(Compound 5-14)

Metallic sodium (1 mmol) was dissolved in dry methanol (8 ml) and *o*-fluorophenyl-di-*p*-fluorophenylmethyl sulfide (0.91 mmol) was added at room temperature under Argon. After stirring for 15 min, *N,N*-diethyl chloroacetamide (1 mmol) was added dropwise. After stirring for another hour at room temperature the reaction mixture was poured into water. Extraction with diethyl ether (3x), drying with sodium sulfate, filtration and concentration gave a residue, which was flash-chromatographed to afford the title compound as a white solid (52%; M.p. 122-123°C).

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-N-methyl-N-phenyl-acetamide (Compound 5-15) was prepared in similar fashion in 43% yield using *N*-methyl-*N*-phenyl chloroacetamide, m.p. 120-121°C.

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-1-piperidin-1-yl-ethanone (Compound 5-16) was prepared in similar fashion in 42% yield using piperidiny chloroacetamide, m.p. 128-129°C.

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-acetamide (Compound 5-17) was prepared in similar fashion in 63% yield using iodoacetamide, THF as solvent and K₂CO₃ as base, m.p. 119-120°C.

2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-propionamide (Compound 5-18) was prepared in similar fashion in 28% yield using acrylamide, m.p. 133-134°C.

[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-acetonitrile (Compound 5-19)

A solution of chloroacetonitrile (5.45 mmol) was added dropwise to a stirring mixture of *o*-fluorophenyl-di-*p*-fluorophenylmethyl sulfide (4.54 mmol) and potassium carbonate (9.1 mmol) in THF (20 ml) at room temperature under Argon. After stirring for 2.5 hours at room temperature, 3.5 hours at 40°C and 2 hours at 60°C the mixture was poured into ice-cold water. Extraction with ethyl ether (3x), drying of the combined organic extracts (Na₂SO₄), filtration, concentration and flash-chromatography of the residue gave the title compound (41%; M.p. 111-112°C).

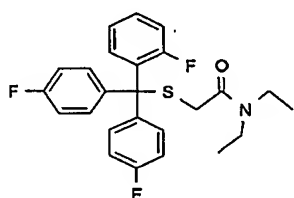
[(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methylsulfanyl]-acetic acid (Compound 5-20)

A solution of di-*p*-fluorophenyl-*o*-fluorophenylcarbinol (0.2 g) was dissolved in trifluoroacetic acid (3 ml) and treated with mercaptoacetic acid (0.5 ml) at room temperature. After stirring for 4 hours at room temperature the reaction was poured into water. Extraction with ethyl ether (3x), drying of the combined organic extracts (Na₂SO₄), filtration, concentration and flash-chromatography of the residue gave the title compound (69%; M.p. 112-113°C).

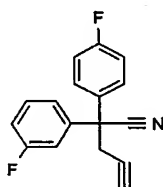
2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-thioacetamide (Compound 5-21)

A solution of 2-[bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-acetamide (0.5 g) in toluene (20 ml) was treated with Lawesson's reagent (0.26 g) at room temperature under Argon and stirred for 1.5 hours at 80°C. After pouring into saturated brine the organics were extracted with dichloromethane (3x). Drying of the combined organic extracts (Na₂SO₄), filtration, concentration and flash-chromatography of the residue gave the title compound (42%; Isolated as an oil).

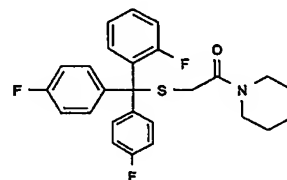
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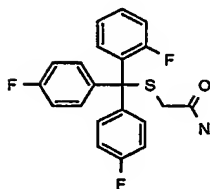
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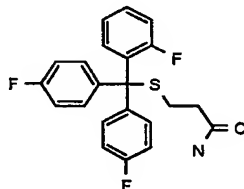
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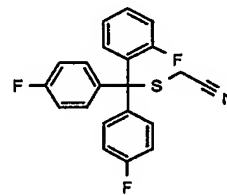
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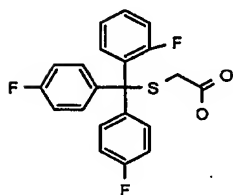
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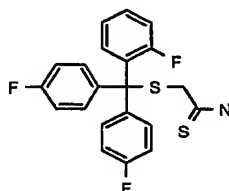
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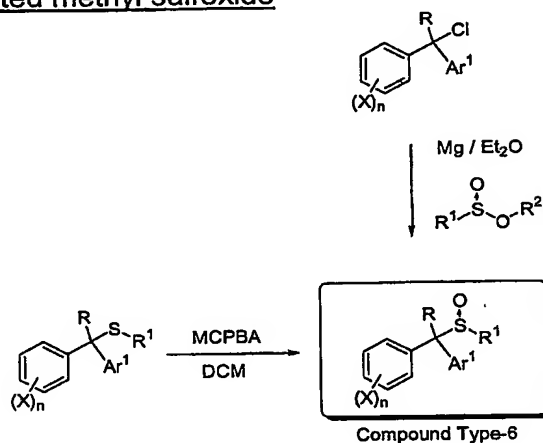
5-19



5-20



5-21

General method for the preparation of compound Type 6Synthesis of tri substituted methyl sulfoxide

A compound Type 5 is dissolved in dichloromethane (DCM) (3mL/mmol), cooled to -5°C, and 3-chloroperoxybenzoic acid (MCPBA) (1.0 equivalent) is added in small portions over 30 minutes. After 30 minutes at room temperature the reaction mixture is poured into water and extracted with DCM, dried with magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (benzin:ethyl acetate) affording a compound Type 6 in 80-95% yield.

In this way the following tri substituted methyl sulfoxides are obtained:

Methyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-1);

Ethyl (bis(4-fluorophenyl)phenyl)methyl sulfoxide (Compound 6-2);

Cyclohexylmethyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-3);

Cyclohexyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-4);

Isopropyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-5);

(2-Thiazolyl)methyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-6);

Phenyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-7);

1-Methyl-2-imidazolyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-8);

2-Pyridyl tris(4-fluorophenyl)methyl sulfoxide (Compound 6-9);

(Cyclohexyl-bis(4-fluorophenyl))methyl phenyl sulfoxide (Compound 6-10);

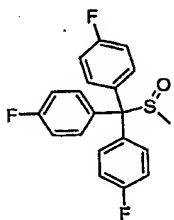
(Cyclopentyl-bis(4-fluorophenyl))methyl methyl sulfoxide (Compound 6-11);

and

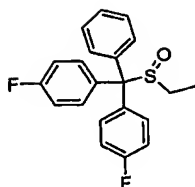
(Cyclohexyl-(4-fluorophenyl)-(2-thiazolyl))methyl methyl sulfoxide

(Compound 6-12).

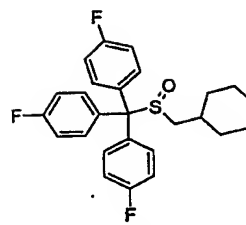
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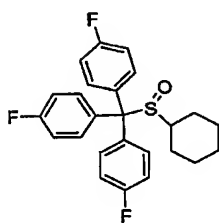
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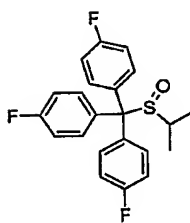
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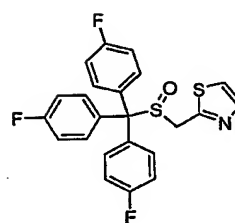
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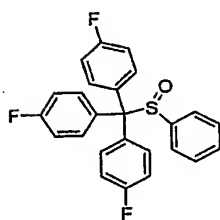
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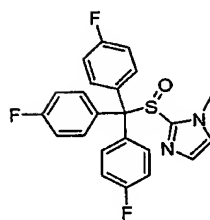
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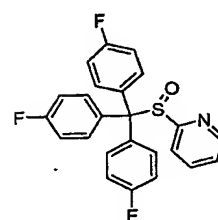
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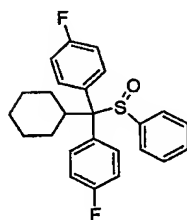
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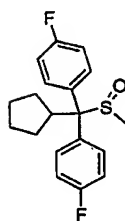
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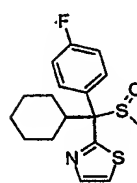
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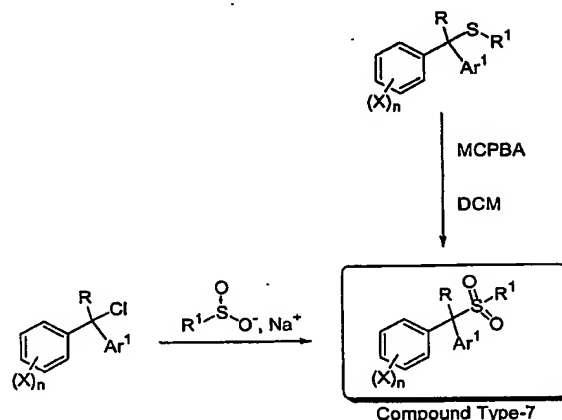
6-10



6-11



6-12

General method for the preparation of compound Type 7Synthesis of sulfone

To a solution of a compound Type 2 and a sodium sulphinate (1.5
 5 equivalent) in dimethyl sulfoxide (DMSO) (2 mL/mmol) is heated to 60°C for 4 hours.
 The reaction mixture is poured into water, extracted with diethyl ether, dried with
 sodium sulfate, filtrated and the solvent removed under reduced pressure to give 80-
 88% yield. The crude product is purified by crystallization from acetic acid to give 45-
 55% yield.

10 In this way the following sulfones are obtained:

Methyl tris(4-fluorophenyl)methyl sulfone (Compound 7-1); Mp. 140.6-
 145.3°C;

Ethyl (bis(4-fluorophenyl)phenyl)methyl sulfone (Compound 7-2);

Cyclohexylmethyl tris(4-fluorophenyl)methyl sulfone (Compound 7-3);

15 Cyclohexyl tris(4-fluorophenyl)methyl sulfone (Compound 7-4);

Isopropyl tris(4-fluorophenyl)methyl sulfone (Compound 7-5);

(2-Thiazolyl)methyl tris(4-fluorophenyl)methyl sulfone (Compound 7-6);

Phenyl tris(4-fluorophenyl)methyl sulfone (Compound 7-7); Mp. 157.4-
 160.6°C;

20 1-Methyl-2-imidazolyl tris(4-fluorophenyl)methyl sulfone (Compound 7-8);

2-Pyridyl tris(4-fluorophenyl)methyl sulfone (Compound 7-9);

(Cyclohexyl-bis(4-fluorophenyl))methyl phenyl sulfone (Compound 7-10);

(Cyclopentyl-bis(4-fluorophenyl))methyl methyl sulfone (Compound 7-11);

(Cyclohexyl-(4-fluorophenyl)-(2-thiazolyl))methyl methyl sulfone (Compound

25 7-12);

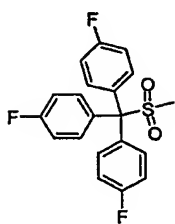
((2-Fluorophenyl)-bis(4-fluorophenyl)-phenyl)methyl methyl sulfone

(Compound 7-13); and

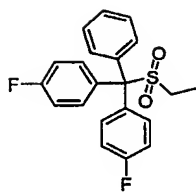
Methanesulphonyl-2-fluorophenyl-bis-(4-fluoro-phenyl) methane

(Compound 7-14); (76%; M.p. 147-149°C).

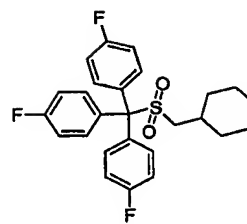
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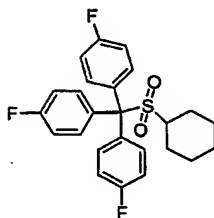
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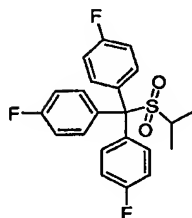
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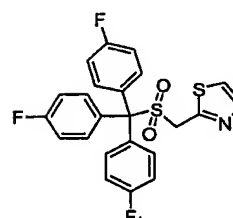
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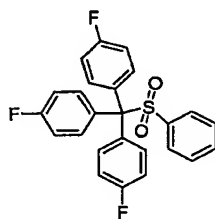
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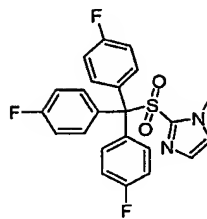
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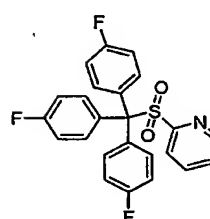
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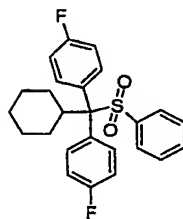
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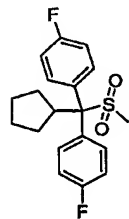
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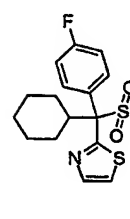
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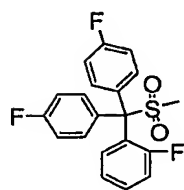
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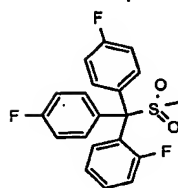
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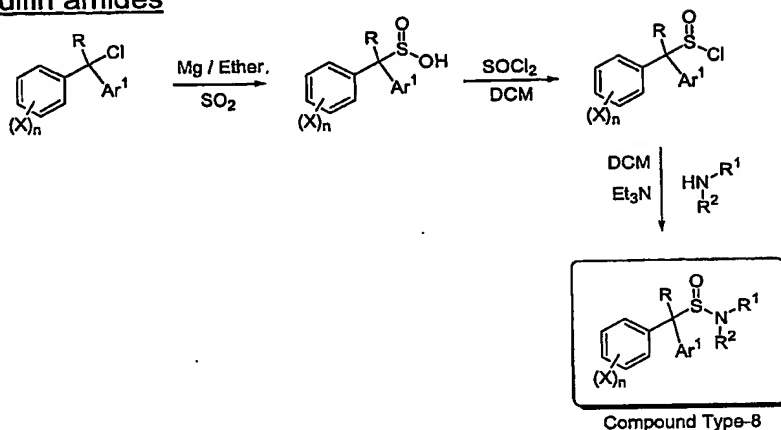
7-12



7-13



7-14

General method for the preparation of compound Type 8Synthesis of sulfin amides

Magnesium turnings in anhydrous diethyl ether is heated to gentle reflux, and a solution of compound Type 2 (1 equivalent) in anhydrous diethyl ether is added slowly from a dropping funnel at such a rate that gentle reflux continue without further heating. When the addition is completed, the reaction mixture is heated to gentle reflux until only traces of unreacted magnesium remains. This Grignard reagent is used in the next step.

Anhydrous diethyl ether in a 3-neck flask is cooled in an acetone/CO₂ bath. The flask is fitted with a SO₂ inlet adaptor, a dropping funnel with the Grignard reagent and an outlet gas trap with aq. NaOH.

SO₂ is condensed, in the cooled ether, by a gentle flux through the outlet gas trap. The Grignard reagent is added drop wise from the funnel during 1 hour.

The sulfinic acid is liberated by acidic work-up and is dissolved in dichloromethane (10ml/g). Thionyl chloride (1 equivalent) is added and the mixture is heated to reflux until the evolution of gasses ceases. The reaction mixture is cooled in an ice bath and a solution of the appropriate amine (2 equivalents) in dichloromethane is added. The resulting mixture is stirred at ambient or elevated temperature until completion of the reaction.

In this way the following sulfin amides are obtained:

Tris-(4-fluorophenyl)-methanesulfinic acid amide (Compound 8-1);

Bis-(4-fluorophenyl)-phenyl-methanesulfinic acid methylamide (Compound 8-2);

Tris-(4-fluorophenyl)-methanesulfinic acid cyclohexylamide (Compound 8-3);

1-[Tris-(4-fluorophenyl)-methanesulfinyl]-piperidine (Compound 8-4);

Tris-(4-fluorophenyl)-methanesulfinic acid dimethylamide (Compound 8-5);

Tris-(4-fluorophenyl)-methanesulfinic acid thiazol-2-ylamide (Compound 8-6);

Tris-(4-fluorophenyl)-methanesulfinic acid (4-fluorophenyl)-amide (Compound 8-7);

Bis-(4-fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanesulfinic acid
methylamide (Compound 8-8);

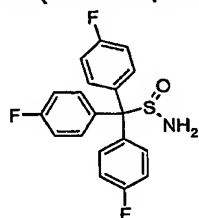
Cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methanesulfinic acid amide (Compound
8-9);

5 Bis-(4-fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanesulfinic acid amide
(Compound 8-10);

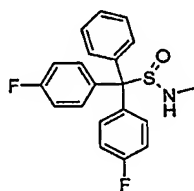
Bis-(4-fluorophenyl)-thiazol-2-yl-methanesulfinic acid amide (Compound 8-11);

and

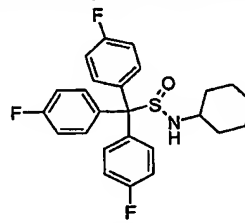
Bis-(4-fluorophenyl)-oxazol-2-yl-methanesulfinic acid amide (Compound 8-12).



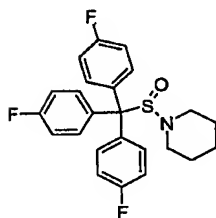
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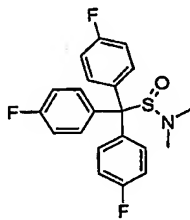
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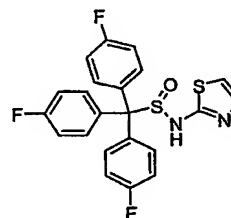
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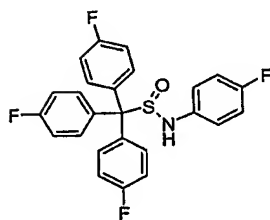
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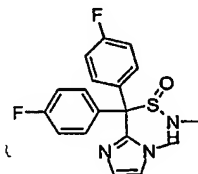
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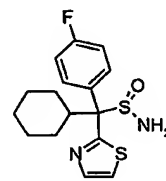
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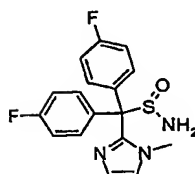
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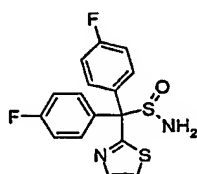
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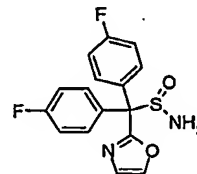
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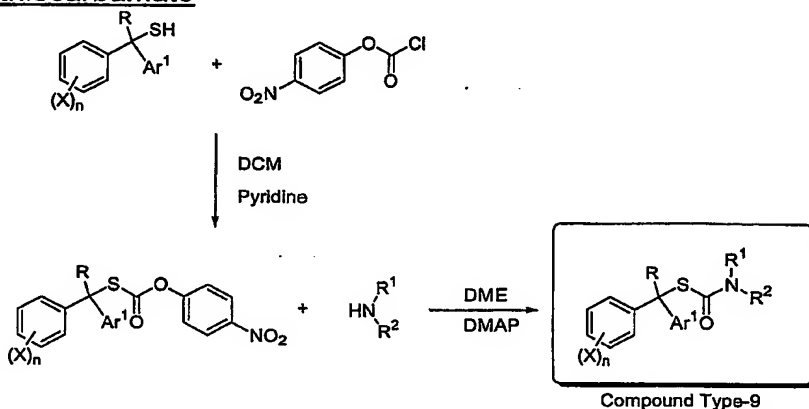
8-10



8-11



8-12

General method for the preparation of compound Type 9Synthesis of thiocarbamate

A compound Type 3 is dissolved in dichloromethane (DCM) (3 mL/mmol),
 5 pyridine (1 equivalent) and 4-nitrophenyl chloroformate (1 equivalent) are added and the solution is heated to reflux for 3 hours. The reaction mixture is cooled, washed with aq. hydrochloric acid, 10% sodium carbonate and water. Dried with magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography affording substituted thiocarbonate.

10 The substituted thiocarbonate is dissolved in dimethoxyethane (DME) (3 mL/mmol), and the amine is added (1 equivalent) together with 4-dimethylaminopyridine (DMAP) (1 equivalent). The reaction mixture is heated for 14 hours at 50°C, cooled to room temperature, washed with aq. hydrochloric acid, 10% sodium carbonate and water. Dried with magnesium sulfate, filtered and the solvent
 15 removed under reduced pressure. The crude product is purified by column chromatography affording substituted thiocarbamate.

In this way the following thiocarbamates are obtained:

- Thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester (Compound 9-1);
- Thiocarbamic acid S-[cyclohexyl-bis-(4-fluorophenyl)-methyl] ester (Compound 9-2);
- 20 Thiocarbamic acid S-[cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methyl] ester (Compound 9-3);
- Piperidine-1-carbothioic acid S-[tris-(4-fluorophenyl)-methyl] ester (Compound 9-4);
- Methyl-thiocarbamic acid S-[cyclopentyl-bis-(4-fluorophenyl)-methyl] ester (Compound 9-5);
- 25 Pyrrolidine-1-carbothioic acid S-[cyclohexyl-bis-(4-fluorophenyl)-methyl] ester (Compound 9-6);
- Methyl-thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester (Compound 9-7);
- Methyl-thiocarbamic acid S-[cyclopentyl-(2-fluorophenyl)-(4-fluorophenyl)-methyl] ester (Compound 9-8);

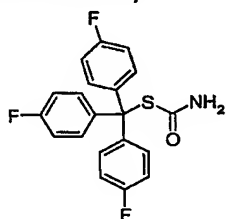
Thiocarbamic acid S-[cyclohexyl-(4-fluorophenyl)-pyridin-2-yl-methyl] ester
(Compound 9-9);

Dimethyl-thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester (Compound 9-10);

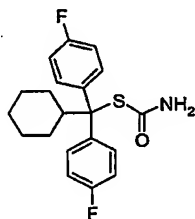
Thiocarbamic acid S-[(2-fluorophenyl)-bis-(4-fluorophenyl)-methyl] ester

5 (Compound 9-11); and

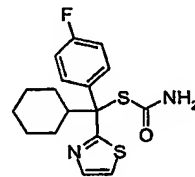
Thiocarbamic acid S-[(2-fluorophenyl)-(4-fluorophenyl)-phenyl-methyl] ester
(Compound 9-12).



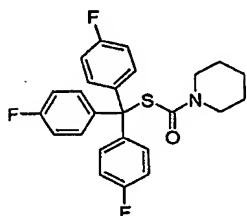
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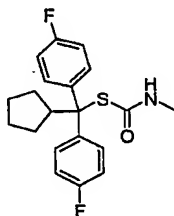
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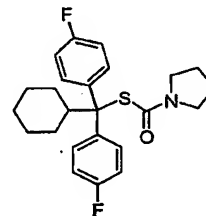
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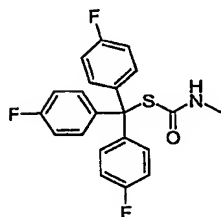
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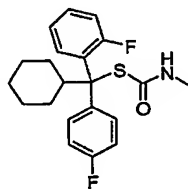
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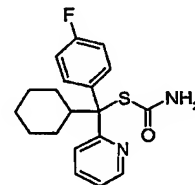
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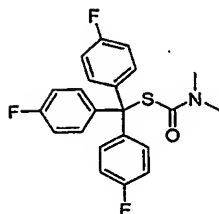
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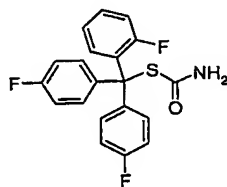
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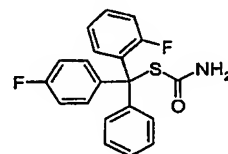
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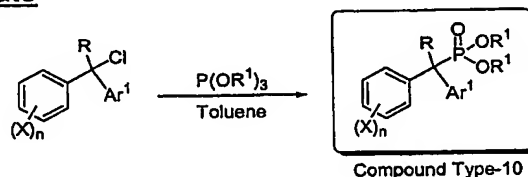
9-10



9-11



9-12

General method for the preparation of compound Type 10Synthesis of phosphonate

5 A compound Type 2 in toluene (2 mL/mmol) and trialkyl phosphite (4 equivalent) is heated at reflux for 16 hours under a nitrogen atmosphere. The reaction mixture is cooled and the volatiles are removed under reduced pressure. The crude product is purified by column chromatography (benzin:ethyl acetate) (20:1) or by crystallization from benzin, affording alkyl phosphonate in 61-82% yield.

10 In this way the following phosphonates are obtained:

[Tris-(4-fluorophenyl)-methyl]-phosphonic acid dimethyl ester (Compound 10-1); Mp. 131.6°C;

[(2-Fluorophenyl)-bis-(4-fluorophenyl)-methyl]-phosphonic acid dimethyl ester (Compound 10-2); Mp. 136.6°C;

15 [(3-Fluorophenyl)-bis-(4-fluorophenyl)-methyl]-phosphonic acid dimethyl ester (Compound 10-3);

2-[Tris-(4-fluorophenyl)-methyl]-[1,3,2]dioxaphospholane 2-oxide (Compound 10-4);

[Cyclohexyl-bis-(4-fluorophenyl)-methyl]-phosphonic acid dimethyl ester (Compound 10-5);

20 [Cyclopentyl-bis-(4-fluorophenyl)-methyl]-phosphonic acid dipropyl ester (Compound 10-6);

[(4-Chlorophenyl)-bis-(4-fluorophenyl)-methyl]-phosphonic acid dimethyl ester (Compound 10-7);

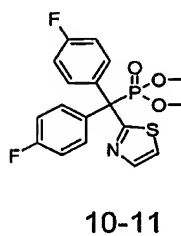
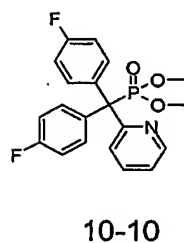
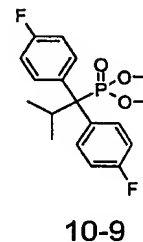
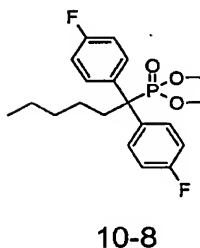
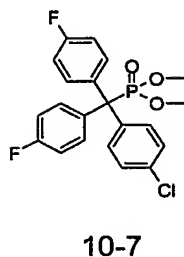
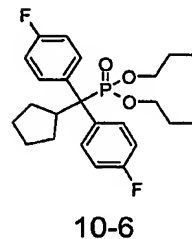
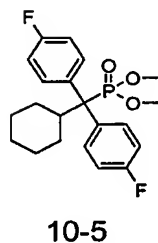
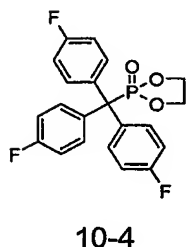
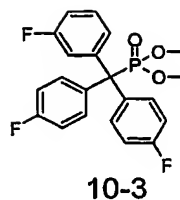
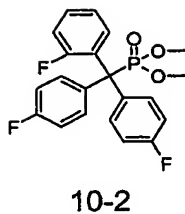
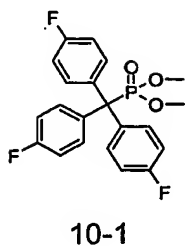
25 [1,1-Bis-(4-fluorophenyl)-hexyl]-phosphonic acid dimethyl ester (Compound 10-8);

[1,1-Bis-(4-fluorophenyl)-2-methyl-propyl]-phosphonic acid dimethyl ester (Compound 10-9);

30 [Bis-(4-fluorophenyl)-pyridin-2-yl-methyl]-phosphonic acid dimethyl ester (Compound 10-10); and

[Bis-(4-fluorophenyl)-thiazol-2-yl-methyl]-phosphonic acid dimethyl ester (Compound 10-11).

69



[(2-Chloro-phenyl)-(2-fluoro-phenyl)-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester (Compound 10-12)

- 5 Chloro tri-*p*-fluorophenylmethane (860 mg) dissolved in toluene (15 ml) was treated with trimethylphosphite (449 mg) and the reaction was refluxed for 6 hours. Toluene was evaporated and the crude residue purified by flash chromatography to afford 62% of the dimethyl phosphonate ester of the title compound (97%; M.p. 131,5-132,5°C).

[(4-Chloro-phenyl)-bis-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester (Compound 10-13)

Chloro tri-*p*-fluorophenylmethane (860 mg) dissolved in toluene (15 ml) was treated with trimethylphosphite (449 mg) and the reaction was refluxed for 6 hours.

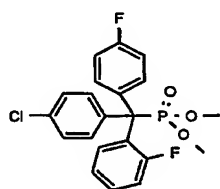
- 5 Toluene was evaporated and the crude residue purified by flash chromatography to afford 62% of the dimethyl phosphonate ester of the title compound (67%; M.p. 136-137°C).

[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methyl]-phosphonic acid (Compound 10-14)

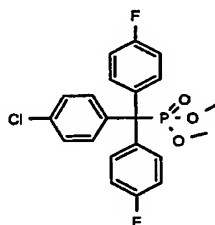
- 10 To a solution of the phosphonate [(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester (195 mg) in acetonitrile (7 ml) was added iodotrimethylsilane (0.17 ml) under Argon. The reaction mixture was left stirring for 3 hrs and then the volatiles were evaporated. 10 ml each of water and chloroform were added to the residue and the mixture was stirred for a further 30 min. The organic
- 15 phase was separated and the water layer was extracted twice more with CHCl_3 . Drying of the combined organic extracts with MgSO_4 , filtration, concentration and recrystallisation of the residue from acetonitrile afforded a white solid (100 mg; M.p. 228-230°C).

[Bis-(4-fluoro-phenyl)-*p*-tolyl-methyl]-phosphonic acid (Compound 10-15)

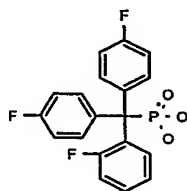
- 20 was prepared in similar fashion in 72% yield, m.p. 240°C (decomposes).



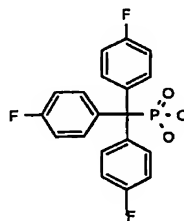
10- 12



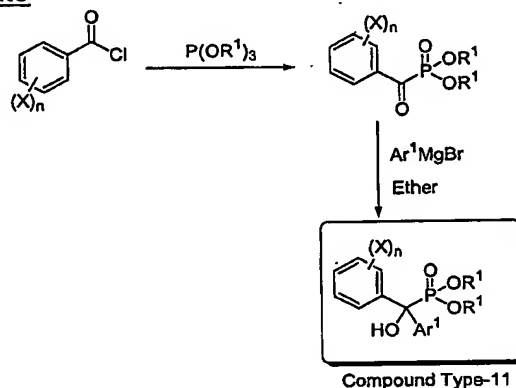
10- 13



10- 14

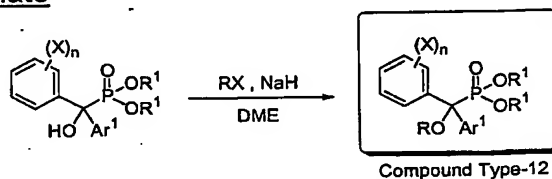


10- 15

General method for the preparation of compound Type 11Synthesis of phosphonate

A substituted benzoyl chloride is cooled to 10°C and trialkyl phosphite (1.1 equivalent) is added slowly from a dropping funnel during 2 hours, with vigorous stirring under nitrogen. An exothermic reaction with evolution of alkyl chloride gas takes place, and the reaction temperature is maintained below 30°C (ice/water bath). The reaction is completed at room temperature for 3-5 hours with a gentle flux of nitrogen, and then distilled at reduced pressure (10^{-2} Torr) to give substituted dialkyl benzoylphosphonates in 69-95% yield.

The substituted dialkyl benzoylphosphonates prepared as described above is added to a fresh prepared Grignard reagent (1.1 equivalent) in ether at -78°C. After 15 minutes the reaction mixture is poured into 0.1 M HCl, extracted with diethyl ether, dried with sodium sulfate, filtrated and the solvent removed under reduced pressure to give crude product. The crude product is purified by column chromatography (benzin:ethyl acetate) or by crystallization from benzin, affording Type 11 compound in 45-60% yield.

General method for the preparation of compound Type 1220 Synthesis of phosphonate

A compound of Type 11 is deprotonated by treatment with sodium hydride (1 equivalent) in dichloromethane. The resulting alcoholate ion is alkylated by treatment with the appropriate alkyl halide under standard conditions.

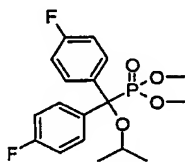
25 In this way the following phosphonates are obtained:

[Bis-(4-fluorophenyl)-isopropoxy-methyl]-phosphonic acid dimethyl ester (Compound 12-1);

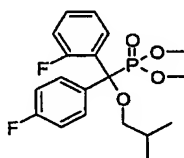
[(2-Fluorophenyl)-(4-fluorophenyl)-isobutoxy-methyl]-phosphonic acid dimethyl ester (Compound 12-2); and

2-[Bis-(4-fluorophenyl)-isopropoxy-methyl]-[1,3,2]-dioxaphospholane 2-oxide (Compound 12-3).

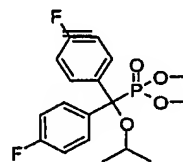
5



12-1



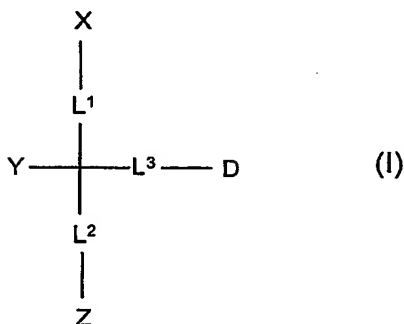
12-2



12-3

CLAIMS:

1. A chemical compound characterized by the general Formula I



5

any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, wherein

X and Y, independently of each another, represent a mono- or polycyclic, carbocyclic and/or heterocyclic group, which carbocyclic or heterocyclic groups optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, alkoxy-alkoxy-carbonyl, a malonic acid dialkyl ester, a diphenyl methyl group, or a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

L^1 and L^2 , independently of each another, may be absent or represent divalent alkyl, alkenyl, alkynyl, O, S or NR^9 ; wherein

R^9 represents hydrogen, alkyl, alkoxy or aryl; and

L^3 may be absent or represents a linker of the formula $-(CH_2)_n-Y-(CH_2)_m-$, wherein

n and m, independently of each another, represent 0, 1, 2, 3 or 4; and

Y is absent or represents O, S, NR^9 , wherein

R^9 represents hydrogen, alkyl, alkoxy or aryl; and

D represents alkyl, cycloalkyl, alkenyl, alkynyl or haloalkyl, or a group of the formula

$-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$,
 $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$,
 $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$,
 $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$,
 $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$,
 $-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$,
 $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

D represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl and heteroaryl, and/or a group of the formula

$-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$,
 $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$, $-R^6-C(=O)OR^4$,
 $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$, $-R^6-C(=O)NR^5(OR^4)$,
 $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$, $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$,
 $-R^6-C(=O)NR^5R^4$, $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$,
 $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$,
 $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

D represents $-S-R^1$, $-S(=O)-R^1$, $-S(=O)_2-R^1$, $-S(=O)-NR^2R^3$, $-S-C(=O)-R^1$, $-S-C(=O)-NR^2R^3$, $-O(C=O)-R^1$, $-O(C=O)-NR^2R^3$, $-N(C=O)-R^1$, $-N(C=O)-NR^2R^3$, $-P(R^2R^3)$, $-P(=O)-R^1$, $-P(=O)-(R^2R^3)$, $-P(=O)_2-(R^2R^3)$; wherein

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, heteroaryl or heteroaryl-alkyl, which aromatic groups may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or a group of the formula

$-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$,
 $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$,
 $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$,
 $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$,
 $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$,
 $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$,
 $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$,
 $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen, hydroxy, alkyl or alkoxy; or

R^2 and R^3 , together with the phosphor atom to which they are bound, represent a heterocyclic ring; or

R^1 represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl, heteroaryl and/or a group of the formula

$-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$,
 $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$,

$-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$,
 $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$,
 $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-C(=O)NR^5R^4$, $-R^6-NR^5C(=O)R^4$,
 $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$,
 $-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$,
 $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein
 R^4 , R^5 and R^7 , independently of each another, represent hydrogen,
 alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic
 group may optionally be substituted once or twice with with halogen,
 alkyl, CF_3 , nitro and/or cyano; or
 R^4 and R^5 , together with the atoms to which they are bound, form a
 heterocyclic ring, and R^7 is as defined above; and
 R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl,
 cycloalkyl, aryl and heteroaryl; and
 R^2 and R^3 , independently of each another, represent hydrogen, alkyl or
 alkoxy.

2. The chemical compound of claim 1, wherein

L^1 and L^2 are absent; and

L^3 is absent or represents a linker of the formula -Y-, wherein

Y represents O, S or NR^9 , wherein

R^9 represents hydrogen or alkyl; and

D represents $-S-R^1$, $-S(=O)-R^1$, $-S(=O)_2-R^1$, $-S(=O)-NR^2R^3$, $-S-C(=O)-R^1$, $-S-C(=O)-NR^2R^3$, $-O(C=O)-R^1$, $-O(C=O)-NR^2R^3$, $-N(C=O)-R^1$, $-N(C=O)-NR^2R^3$, $-P-(R^2R^3)$, $-P(=O)-R^1$, $-P(=O)-(R^2R^3)$, $-P(=O)_2-(R^1)_2$ or $-P(=O)-(OR^1)_2$; wherein

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, haloalkyl, or
 a group of the formula

$-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$,
 $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$,
 $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$,
 $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$,
 $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-NR^5C(=O)R^4$, $-R^6-NR^7C(=O)NR^5R^4$,
 $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$, $-R^6-CH[C(=S)R^4]_2$,
 $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$, $-R^6-CH[C(=O)SR^4]_2$,
 $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen, hydroxy, alkyl or alkoxy; or

R^2 and R^3 , together with the phosphor atom to which they are bound, represent a heterocyclic ring; or

R^1 represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, cycloalkyl, alkenyl, alkynyl, halogen, haloalkyl, aryl, heteroaryl and/or a group of the formula

$-R^6-NR^5R^4$, $-R^6-NO_2$, $-R^6-OR^4$, $-R^6-SR^4$, $-R^6-S(=O)NR^5R^4$, $-R^6-S(=O)R^4$,
 $-R^6-S(=O)_2R^4$, $-R^6-S(=O)_2OR^4$, $-R^6-S(=O)_2NR^5R^4$, $-R^6-NR^5S(=O)_2R^4$,
 $-R^6-NR^7S(=O)_2NR^5R^4$, $-R^6-CN$, $-R^6-C(=NR^5)R^4$, $-R^6-C(=NNR^5)R^4$,
 $-R^6-C(=NOR^5)R^4$, $-R^6-C(=O)R^4$, $-R^6-C(=O)NR^5R^4$, $-R^6-C(=S)R^4$,
 $-R^6-C(=O)OR^4$, $-R^6-C(=S)OR^4$, $-R^6-C(=O)SR^4$, $-R^6-C(=S)SR^4$,
 $-R^6-C(=O)NR^5(OR^4)$, $-R^6-C(=S)NR^5(OR^4)$, $-R^6-C(=O)NR^5(SR^4)$,
 $-R^6-C(=S)NR^5(SR^4)$, $-R^6-CH(CN)_2$, $-R^6-C(=O)NR^5R^4$, $-R^6-NR^5C(=O)R^4$,
 $-R^6-NR^7C(=O)NR^5R^4$, $-R^6-C(=S)NR^5R^4$, $-R^6-CH[C(=O)R^4]_2$,
 $-R^6-CH[C(=S)R^4]_2$, $-R^6-CH[C(=O)OR^4]_2$, $-R^6-CH[C(=S)OR^4]_2$,
 $-R^6-CH[C(=O)SR^4]_2$, $-R^6-CH[C(=S)SR^4]_2$ or $-R^6-CH[C(=S)NR^5R^4]_2$; wherein

R^4 , R^5 and R^7 , independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF_3 , nitro and/or cyano; or

R^4 and R^5 , together with the atoms to which they are bound, form a heterocyclic ring, and R^7 is as defined above; and

R^6 is absent or represents a linker selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; and

R^2 and R^3 , independently of each another, represent hydrogen or alkyl.

3. The chemical compound of either of claims 1-2, wherein

X, Y and Z represent a phenyl group, which phenyl groups, independently of each another, are optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

5 X and Y represent a phenyl group, which phenyl groups, independently of each another, are optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and
Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, halo-alkyl, halo-alkenyl, halo-alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, alkoxy-alkoxy-carbonyl, a
10 malonic acid dialkyl ester or a diphenyl methyl group; or

X and Y represent a phenyl group, which phenyl groups, independently of each another, are optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and
15 Z represents a heteroaryl group, which heteroaryl is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

20 one of X and Y represents a phenyl group, which phenyl group is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and
the other of X and Y represents a heteroaryl group, which heteroaryl is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and
25 Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, halo-alkyl, halo-alkenyl, halo-alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, alkoxy-alkoxy-carbonyl, a malonic acid dialkyl ester or a diphenyl methyl group; or

30 one of X and Y represents a phenyl group, which phenyl group is optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and
Z and the other of X and Y represents a heteroaryl group, which heteroaryl is
35 optionally substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

4. The chemical compound of any of claims 1-3, wherein the heteroaryl group is thiazolyl, in particular 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-

isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl, [1,3,2]dioxaphospholane, or
5 [1,3,2]dioxaphosphinane.

5. The chemical compound of any of claims 1-4, wherein

10 X, Y and Z represent a phenyl group, which phenyl groups, independently of each another, optionally are substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; or

15 X and Y represent a phenyl group, which phenyl groups, independently of each another, optionally are substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; and
Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-
20 carbonyl, malonic acid dialkyl ester or a diphenyl methyl group; or

X and Y represent a phenyl group, which phenyl groups, independently of each another, optionally are substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; and
25 Z represents 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl, 2-pyridinyl or [1,3,2]dioxaphospholane, which aromatic groups may be substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; or

30 one of X and Y represents a phenyl group, which phenyl group is optionally substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; and
35 the other of X and Y represents 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl, 2-pyridinyl or [1,3,2]dioxaphospholane, which aromatic groups may be substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; and

Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl; hydroxy-alkyl, cyano-alkyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, malonic acid dialkyl ester or a diphenyl methyl group; or

- 5 one of X and Y represents a phenyl group, which phenyl group is optionally substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; and
- 10 Z and the other of X and Y represents 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl, 2-pyridinyl or [1,3,2]dioxaphospholane, which aromatic groups may be substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano.

6. The chemical compound of claim 5, wherein

D represents a phenyl group, which phenyl group is substituted once or twice with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano; or

D represents a heteroaryl group selected from 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl or 2-pyridinyl, which heteroaryl group may be substituted once or twice with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; hydroxy, nitro and/or cyano; and

L³ is absent or represents a linker of the formula -Y-, wherein

Y represents O or S.

15

7. The chemical compound of any of claims 1-6, wherein the phenyl groups and/or the heteroaryl groups are substituted once or twice with fluoro, chloro, CF₃, nitro and/or cyano.

20

8. The chemical compound of claim 7, which is

2-[Bis-(4-fluoro-phenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-thiazole;

2-[Tris-(4-fluoro-phenyl)-methylsulfanyl]-pyridin-1-ol;

1-Methyl-2-[tris-(4-fluoro-phenyl)-methylsulfanyl]-1H-imidazole;

2-[Tris-(4-fluoro-phenyl)-methylsulfanyl]-pyridine;

25

2-[(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methoxy]-[1,3,2]-dioxaphospholane; or

2-[Tris-(4-fluoro-phenyl)-methoxy]-[1,3,2]-dioxaphospholane;

any of its enantiomers or any mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

9. The chemical compound of any of claims 1-8, wherein

D represents -CN, R^6 -CN, -CON(R^2R^3), -S- R^1 , -S(=O)- R^1 , -S(=O)₂- R^1 , -S-C(=O)- R^1 , -O(C=O)- R^1 , -P-(R^2R^3), -P(=O)(R^2R^3), -P(=O)₂(R^2R^3); wherein

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl or -NR⁵ R^4 ; wherein

R^4 and R^5 , independently of each another, represent hydrogen, alkyl, cycloalkyl, aryl or heteroaryl, which aromatic group may optionally be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R^4 and R^5 , together with the N atom to which they are bound, form a pyrrolidine or piperidine ring; or

R^1 represents aryl, aralkyl, heteroaryl, heteroaryl-alkyl, which aromatic groups may optionally be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; and

R^2 and R^3 , independently of each another, represent hydrogen, hydroxy, alkyl or alkoxy; or

R^2 and R^3 , together with the phosphor atom to which they are bound, represent a heterocyclic ring selected from [1,3,2]dioxaphospholane and [1,3,2]dioxaphosphinane; and

R^6 is absent or represents alkyl.

- 5 10. The chemical compound of any of claims 1-9, wherein L³ is absent or represents -O- or -S-.

11. The chemical compound of either of claims 9-10, wherein

10 X and Y represent a phenyl group, which phenyl groups, independently of each another, optionally are substituted one or more times with halogen, in particular fluoro and/or chloro; alkyl, in particular methyl, ethyl, propyl and/or isopropyl; haloalkyl, in particular CF₃; nitro and/or cyano;

15 Z represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, cyano-alkyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, alkoxy-alkoxy-alkyl, acyl, alkoxy-carbonyl, malonic acid dialkyl ester or a diphenyl methyl group; and

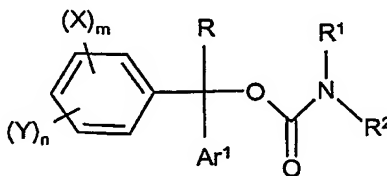
D represents -CN, R^6 -CN, -CON(R^2R^3), wherein

R^2 and R^3 , independently of each another, represent hydrogen or alkyl; and R^6 represents alkyl.

12. The chemical compound of claim 10, which is

- 5 2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-enenitrile;
 2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3-methyl-butyronitrile;
 2,2-Bis-(4-fluoro-phenyl)-3-methyl-butyronitrile;
 2,2-Bis-(4-fluoro-phenyl)-4-methyl-pentanenitrile;
 2,2-Bis-(4-fluoro-phenyl)-pent-4-enenitrile;
 10 2,2-Bis-(4-fluoro-phenyl)-pent-4-yenenitrile;
 2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-yenenitrile;
 2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-4-methyl-pentanenitrile;
 2,2-Bis-(4-fluoro-phenyl)-3,3-diphenyl-propionitrile;
 2-(2-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3,3-diphenyl-propionitrile;
 15 2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-3-methyl-butyronitrile;
 2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-4-methyl-pentanenitrile;
 2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-enenitrile;
 2-(3-Fluoro-phenyl)-2-(4-fluoro-phenyl)-pent-4-yenenitrile;
 2,2-Bis-(4-fluoro-phenyl)-3-oxo-butyronitrile;
 20 3-Ethoxy-2-(4-fluoro-phenyl)-2-(2-fluoro-phenyl)-propionitrile;
 3-Cyano-3-(4-fluoro-phenyl)-3-(2-fluoro-phenyl)-propionic acid ethyl ester;
 3-Ethoxy-2,2-bis-(4-fluoro-phenyl)-propionitrile;
 3-Cyano-3,3-bis-(4-fluoro-phenyl)-propionic acid ethyl ester;
 Cyano-(4-fluoro-phenyl)-(2-fluoro-phenyl)-acetic acid methyl ester;
 25 2-[Cyano-bis-(4-fluoro-phenyl)-methyl]-malonic acid diethyl ester;
 2,2-Bis-(4-fluoro-phenyl)-4-hydroxy-butyronitrile;
 2,2-Bis-(4-fluoro-phenyl)-3-(2-methoxy-ethoxy)-propionitrile;
 2,2-Bis-(4-fluoro-phenyl)-succinonitrile; or
 2,2-Bis-(4-fluoro-phenyl)-3-methyl-butyramide;
 30 any of its enantiomers or any mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

13. The chemical compound of claim 1, represented by the following Formula IV (Type 4)



wherein

m is 0, 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl,
5 hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which
carbocyclic or heterocyclic group optionally may be substituted one or more
times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
and/or cyano; and

10 R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or
heterocyclic group, which carbocyclic or heterocyclic group optionally may be
substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-
15 alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen or alkyl; or
R¹ and R², together with the N atom to which they are bound, form a 5- to 7-
membered heterocyclic ring.

20 14. The chemical compound of claim 13, wherein

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro
and/or cyano;

25 Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl;
isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-
imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or
5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2,
4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which
30 aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl,
hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl;
isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-
imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or
35 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2,
4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which
aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl,
hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen or alkyl; or

R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

15. The chemical compound of claim 14, wherein

m is 0 or 1;

n is 0 or 1;

10 X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

Ar¹ represents phenyl, which may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

15 Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R¹ and R², independently of each another, represent hydrogen or alkyl; or

20 R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

16. The chemical compound of claim 15, wherein

m is 0 or 1;

n is 0 or 1;

25 X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro and/or cyano;

Ar¹ represents phenyl, which may be substituted once or twice with fluoro, chloro, CF₃, nitro and/or cyano;

30 Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, CF₃, nitro and/or cyano; or

R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and

R¹ and R², independently of each another, represent hydrogen or alkyl; or

35 R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

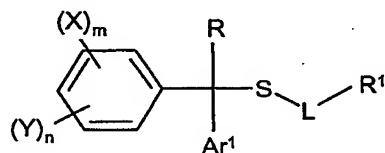
17. The chemical compound of claim 16, which is

(±)-Carbamic acid tris-(4-fluorophenyl)-methyl ester;

(±)-Carbamic acid cyclohexyl-bis-(4-fluorophenyl)-methyl ester;

(±)-Carbamic acid cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methyl ester;
 (±)-Piperidine-1-carboxylic acid tris-(4-fluorophenyl)-thiazol-2-yl-methyl ester;
 (±)-Methyl-carbamic acid cyclopentyl-bis-(4-fluorophenyl)-methyl ester;
 (±)-Pyrrolidine-1-carboxylic acid cyclohexyl-bis-(4-fluorophenyl)-methyl ester;
 5 (±)-Methyl-carbamic acid tris-(4-fluorophenyl)-methyl ester;
 (±)-Methyl-carbamic acid cyclohexyl-(2-fluorophenyl)-(4-fluorophenyl)-methyl ester;
 (±)-Carbamic acid cyclohexyl-(4-fluorophenyl)-pyridin-2-yl-methyl ester;
 (±)-Dimethyl-carbamic acid tris-(4-fluorophenyl)-methyl ester;
 10 (±)-Carbamic acid (2-fluorophenyl)-bis-(4-fluorophenyl)-methyl ester; or
 (±)-Carbamic acid (2-fluorophenyl)-(4-fluorophenyl)-phenyl-methyl ester;
 any of its enantiomers or any mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

- 15 18. The chemical compound of claim 1, represented by the following Formula V (Type 5)



wherein

n is 1 or 2;

20 m is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more
 25 times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
 30 halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkenyl or halo-alkynyl; and

L is absent or represents alkyl; and

R¹ represents alkyl, cycloalkyl or cycloalkyl-alkyl, -CN, -C(=O)OR⁴,

35 -C(=O)N(R⁴R⁵), -C(=S)N(R⁴R⁵), wherein R⁴ and R⁵, independently of each another, represent hydrogen, alkyl or phenyl, or R⁴ and R⁵, together with the

nitrogen atom form a heterocyclic ring selected from pyrrolidinyl and piperidinyl, or a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

5 19. The chemical compound of claim 18, wherein

n is 1;

m is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

10 Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

15 Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

20 R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkenyl or halo-alkynyl; and

L is absent or represents alkyl; and

R¹ represents alkyl, cycloalkyl or cycloalkyl-alkyl, -CN, -C(=O)OR⁴,

-C(=O)N(R⁴R⁵), -C(=S)N(R⁴R⁵), wherein R⁴ and R⁵, independently of each

30 another, represent hydrogen, alkyl or phenyl, or R⁴ and R⁵, together with the nitrogen atom form a heterocyclic ring selected from pyrrolidinyl and piperidinyl,

or an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl;

oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-

35 isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which

aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

20. The chemical compound of claim 19, wherein

m is 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro
5 and/or cyano;

Ar¹ represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl or 2-
pyridinyl, which aromatic group may be substituted once or twice with halogen,
alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-
10 imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted
once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl or cycloalkyl-alkyl; and

L is absent or represents methylene or ethylene; and

R¹ represents alkyl, cycloalkyl or cycloalkyl-alkyl, -CN, -C(=O)OR⁴,

15 -C(=O)N(R⁴R⁵), -C(=S)N(R⁴R⁵), wherein R⁴ and R⁵, independently of each
another, represent hydrogen, alkyl or phenyl, or R⁴ and R⁵, together with the
nitrogen atom form a heterocyclic ring selected from pyrrolidinyl and piperidinyl,
or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl,
2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or
20 twice with halogen, alkyl, CF₃, nitro and/or cyano.

21. The chemical compound of claim 20, wherein

m is 1;

n is 0 or 1;

25 X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro
and/or cyano;

Ar¹ represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl or 2-
pyridinyl, which aromatic group may be substituted once or twice with halogen,
alkyl, CF₃, nitro and/or cyano;

30 Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-
imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted
once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and

L is absent or represents -CH₂-; and

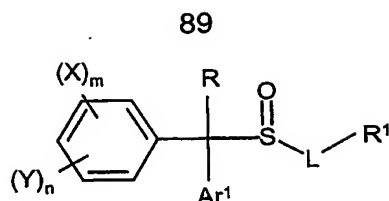
35 R¹ represents cycloalkyl or cycloalkyl-alkyl, -CN, -C(=O)OR⁴, -C(=O)N(R⁴R⁵),
-C(=S)N(R⁴R⁵), wherein R⁴ and R⁵, independently of each another, represent
hydrogen, alkyl or phenyl, or R⁴ and R⁵, together with the nitrogen atom form a
heterocyclic ring selected from pyrrolidinyl and piperidinyl, or an aromatic group
selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-

pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano.

22. The chemical compound of claim 21, which is

5 2-[Cyclohexyl-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfanyl]-thiazole;
2-[(2-Chlorophenyl)-cyclohexyl-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfanyl]-
1-methyl-1*H*-imidazole;
2-[(4-Chlorophenylsulfanyl)-cyclopentyl-(4-fluorophenyl)-(2-fluorophenyl)-methyl]-
pyridine;
10 2-[Cyclohexyl-(3,4-dichlorophenyl)-(1*H*-imidazol-2-yl)-methylsulfanyl]-pyridine;
2-[Cyclopentyl-(2-fluorothiazol-4-yl)-(4-nitro-3-trifluoromethylphenyl)-
methylsulfanyl]-pyridine;
2-[(4-fluorophenyl)-(4-fluorophenylsulfanyl)-(4-nitro-3-trifluoromethylphenyl)-
methyl]-thiazole;
15 2-[Cyclohexylsulfanyl-(4-fluorophenyl)-(4-nitro-3-trifluoromethylphenyl)-methyl]-
thiazole;
2-[Cyclopentylsulfanyl-bis-(4-fluorophenyl)-methyl]-1-methyl-1*H*-imidazole;
4-[Cyclohexylsulfanyl-bis-(4-fluorophenyl)-methyl]-2-fluoro-thiazole;
2-[Bis-(4-fluorophenyl)-(2-fluorophenyl)-methylsulfonyl]-thiazole;
20 1-Methyl-2-[tris-(4-fluorophenyl)-methylsulfanyl]-1*H*-imidazole;
2-[Tris-(4-fluorophenyl)-methylsulfanyl]-pyridine;
2-[Tris-(4-fluorophenyl)-methylsulfanyl]-pyridine-N-oxide;
[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-acetonitrile;
2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-acetamide;
25 [(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methylsulfanyl]-acetic acid;
2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-propionamide;
2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-thioacetamide;
2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-*N,N*-diethyl-acetamide;
or
30 2-[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methylsulfanyl]-1-piperidin-1-yl-
ethanone;
any of its enantiomers or any mixture of enantiomers, or a pharmaceutically
acceptable salt thereof, or an N-oxide thereof.

35 23. The chemical compound of claim 1, represented by the following Formula VI
(Type 6)



wherein

m is 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

L is absent or represents alkyl; and

R¹ represents cycloalkyl, or a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

24. The chemical compound of claim 23, wherein

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-

- imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or
5 R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and
L is absent or represents alkyl; and
R¹ represents cycloalkyl or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may
10 be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano.
25. The chemical compound of claim 24, wherein
m is 0 or 1;
15 n is 0 or 1;
X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro and/or cyano;
Ar¹ represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted
20 once or twice with halogen, alkyl, CF₃, nitro and/or cyano;
Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or
R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl; and
25 L is absent or represents methylene or ethylene; and
R¹ represents cycloalkyl or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, methyl, CF₃, nitro and/or cyano.
- 30 26. The chemical compound of claim 25, wherein
m is 0 or 1;
n is 0 or 1;
X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;
35 Ar¹ represents an aromatic group selected from phenyl and 2-thiazolyl; which aromatic groups may be substituted once or twice with fluoro, CF₃, nitro and/or cyano;
Ar² represents phenyl, which may be substituted once or twice with fluoro, CF₃, nitro and/or cyano; or

R represents cycloalkyl or cycloalkyl-alkyl; and

L is absent or represents $-\text{CH}_2-$; and

R^1 represents cycloalkyl, phenyl, 2-thiazolyl, 2-imidazolyl or 2-pyridinyl, which aromatic groups may be substituted once with fluoro, CF_3 , nitro and/or cyano; or

R^1 represents 2-thiazolyl-methyl.

27. The chemical compound of claim 26, which is

Methyl tris(4-fluorophenyl)methyl sulfoxide;

Ethyl (bis(4-fluorophenyl)phenyl)methyl sulfoxide;

Cyclohexylmethyl tris(4-fluorophenyl)methyl sulfoxide;

Cyclohexyl tris(4-fluorophenyl)methyl sulfoxide;

Isopropyl tris(4-fluorophenyl)methyl sulfoxide;

(2-Thiazolyl)methyl tris(4-fluorophenyl)methyl sulfoxide;

Phenyl tris(4-fluorophenyl)methyl sulfoxide;

1-Methyl-2-imidazolyl tris(4-fluorophenyl)methyl sulfoxide;

2-Pyridyl tris(4-fluorophenyl)methyl sulfoxide;

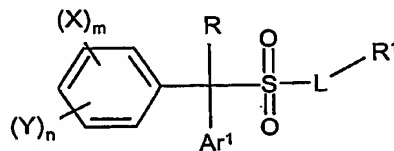
(Cyclohexyl-bis(4-fluorophenyl))methyl phenyl sulfoxide;

(Cyclopentyl-bis(4-fluorophenyl))methyl methyl sulfoxide; or

(Cyclohexyl-(4-fluorophenyl)-(2-thiazolyl))methyl methyl sulfoxide;

any of its enantiomers or any mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

28. The chemical compound of claim 1, represented by the following Formula VII (Type 7)



wherein

m is 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar^1 represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar^2) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be

substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

5 L may be absent or represents alkyl; and

R¹ represents alkyl, cycloalkyl or a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

10

29. The chemical compound of claim 28, wherein

m is 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

15

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

20

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

25

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

30

L may be absent or represents alkyl; and

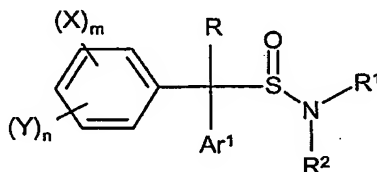
R¹ represents alkyl, cycloalkyl or an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano.

35

30. The chemical compound of claim 29, wherein
m is 1;
n is 0 or 1;
5 X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro
and/or cyano;
Ar¹ represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-
imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted
once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano;
10 Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-
imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted
once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano; or
R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl; and
L may be absent or represents methylene or ethylene; and
15 R¹ represents alkyl, cycloalkyl or an aromatic group selected from phenyl, 2-
thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic
groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro
and/or cyano.
- 20 31. The chemical compound of claim 30, wherein
m is 1;
n is 0 or 1;
X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro
and/or cyano;
25 Ar¹ represents an aromatic group selected from phenyl and 2-thiazolyl, which
aromatic groups may be substituted once or twice with fluoro, chloro, methyl,
CF₃, nitro and/or cyano;
Ar² represents phenyl, which may be substituted once or twice with fluoro, CF₃,
nitro and/or cyano; or
30 R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and
L may be absent or represents methylene; and
R¹ represents alkyl or cycloalkyl; or
R¹ represents phenyl, 2-thiazolyl, 2-imidazolyl or 2-pyridinyl, which aromatic
groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro
35 and/or cyano.
32. The chemical compound of claim 31, which is
Methyl tris(4-fluorophenyl)methyl sulfone;
Ethyl (bis(4-fluorophenyl)phenyl)methyl sulfone;

Cyclohexylmethyl tris(4-fluorophenyl)methyl sulfone;
 Cyclohexyl tris(4-fluorophenyl)methyl sulfone;
 Isopropyl tris(4-fluorophenyl)methyl sulfone;
 (2-Thiazolyl)methyl tris(4-fluorophenyl)methyl sulfone;
 5 Phenyl tris(4-fluorophenyl)methyl sulfone;
 1-Methyl-2-imidazolyl tris(4-fluorophenyl)methyl sulfone;
 2-Pyridyl tris(4-fluorophenyl)methyl sulfone;
 (Cyclohexyl-bis(4-fluorophenyl))methyl phenyl sulfone;
 (Cyclopentyl-bis(4-fluorophenyl))methyl methyl sulfone;
 10 (Cyclohexyl-(4-fluorophenyl)-(2-thiazolyl))methyl methyl sulfone;
 ((2-Fluorophenyl)-bis(4-fluorophenyl)-phenyl)methyl methyl sulfone; or
 Methanesulphonyl-2-fluorophenyl-bis-(4-fluoro-phenyl) methane;
 any of its enantiomers or any mixture of enantiomers, or a pharmaceutically
 acceptable salt thereof, or an N-oxide thereof.

33. The chemical compound of claim 1, represented by the following Formula VIII (Type 8)



wherein

m is 0, 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which

carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or a mono- or polycyclic, carbocyclic or heterocyclic group,

which carbocyclic or heterocyclic groups optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

5 R^1 and R^2 , together with the N atom to which they are bound, form a 5- to 7-membered heterocyclic ring.

34. The chemical compound of claim 33, wherein

m is 0 or 1;

n is 0 or 1;

10 X and Y, independently of each another, represent halogen, alkyl, CF_3 , nitro and/or cyano;

Ar^1 represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar^2 represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

25 R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R^1 and R^2 , independently of each another, represent hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl, or an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

35 R^1 and R^2 , together with the N atom to which they are bound, form a pyrrolidine or piperidine ring.

35. The chemical compound of claim 34, wherein

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

5 Ar¹ represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted
10 once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl, or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be
15 substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or
R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or piperidine ring.

36. The chemical compound of claim 35, wherein

20 m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, CF₃, nitro and/or cyano;

25 Ar¹ represents phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted
once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano; or

30 R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, or 2-oxazolyl, which may be substituted with fluoro, methyl, CF₃, nitro or cyano; or

35 R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or piperidine ring.

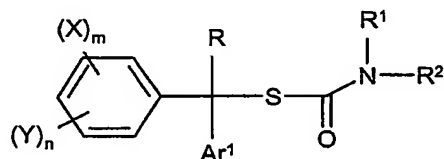
37. The chemical compound of claim 36, which is

Tris-(4-fluorophenyl)-methanesulfinic acid amide;

Bis-(4-fluorophenyl)-phenyl-methanesulfinic acid methylamide;

Tris-(4-fluorophenyl)-methanesulfinic acid cyclohexylamide;
 1-[Tris-(4-fluorophenyl)-methanesulfinyl]-piperidine;
 Tris-(4-fluorophenyl)-methanesulfinic acid dimethylamide;
 Tris-(4-fluorophenyl)-methanesulfinic acid thiazol-2-ylamide;
 5 Tris-(4-fluorophenyl)-methanesulfinic acid (4-fluorophenyl)-amide;
 Bis-(4-fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanesulfinic acid
 methylamide;
 Cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methanesulfinic acid amide;
 Bis-(4-fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanesulfinic acid amide;
 10 Bis-(4-fluorophenyl)-thiazol-2-yl-methanesulfinic acid amide; or
 Bis-(4-fluorophenyl)-oxazol-2-yl-methanesulfinic acid amide;
 any of its enantiomers or any mixture of enantiomers, or a pharmaceutically
 acceptable salt thereof, or an N-oxide thereof.

- 15 38. The chemical compound of claim 1, represented by the following Formula IX
 (Type 9)



wherein

m is 0, 1 or 2;

20 n is 0, 1 or 2;

X and Y, independently of each another, represent alkyl, alkenyl, alkynyl,
 hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which
 carbocyclic or heterocyclic group optionally may be substituted one or more
 25 times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro
 and/or cyano; and

R represents a group (Ar²) which is a mono- or polycyclic, carbocyclic or
 heterocyclic group, which carbocyclic or heterocyclic group optionally may be
 substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
 30 halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-
 alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl,
 cycloalkyl-alkyl and/or a mono- or polycyclic, carbocyclic or heterocyclic group,
 35 which carbocyclic or heterocyclic groups optionally may be substituted one or

more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or
R¹ and R², together with the N atom to which they are bound, form a 5- to 7-membered heterocyclic ring.

5

39. The chemical compound of claim 38, wherein

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

10

Ar¹ represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

15

Ar² represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

20

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

25

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or
R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

30

35

40. The chemical compound of claim 39, wherein

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro and/or cyano;

5 Ar¹ represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

10 R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

15 R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

41. The chemical compound of claim 40, wherein

m is 0 or 1;

20 n is 0 or 1;

X and Y, independently of each another, represent fluoro, CF₃, nitro and/or cyano;

Ar¹ represents phenyl or 2-thiazolyl, which may be substituted once with fluoro, chloro, methyl, CF₃, nitro or cyano;

25 Ar² represents phenyl, which may be substituted once with fluoro, CF₃, nitro or cyano; or

R represents cycloalkyl or cycloalkyl-alkyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and/or an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl; or

30 R¹ and R², together with the N atom to which they are bound, form a pyrrolidine or a piperidine ring.

42. The chemical compound of claim 41, which is

35 Thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester;

Thiocarbamic acid S-[cyclohexyl-bis-(4-fluorophenyl)-methyl] ester;

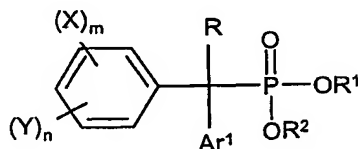
Thiocarbamic acid S-[cyclohexyl-(4-fluorophenyl)-thiazol-2-yl-methyl] ester;

Piperidine-1-carbothioic acid S-[tris-(4-fluorophenyl)-methyl] ester;

Methyl-thiocarbamic acid S-[cyclopentyl-bis-(4-fluorophenyl)-methyl] ester;

Pyrrolidine-1-carbothioic acid S-[cyclohexyl-bis-(4-fluorophenyl)-methyl] ester;
 Methyl-thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester;
 Methyl-thiocarbamic acid S-[cyclopentyl-(2-fluorophenyl)-(4-fluorophenyl)-methyl]
 ester;
 5 Thiocarbamic acid S-[cyclohexyl-(4-fluorophenyl)-pyridin-2-yl-methyl] ester;
 Dimethyl-thiocarbamic acid S-[tris-(4-fluorophenyl)-methyl] ester;
 Thiocarbamic acid S-[(2-fluorophenyl)-bis-(4-fluorophenyl)-methyl] ester; or
 Thiocarbamic acid S-[(2-fluorophenyl)-(4-fluorophenyl)-phenyl-methyl] ester;
 any of its enantiomers or any mixture of enantiomers, or a pharmaceutically
 10 acceptable salt thereof, or an N-oxide thereof.

43. The chemical compound of claim 1, represented by the following Formula X
 (Type 10)



- 15 wherein
 m is 1 or 2;
 n is 0, 1 or 2;
 X and Y, independently of each another, represent alkyl, alkenyl, alkynyl, alkoxy,
 amino, halogen, haloalkyl, nitro and/or cyano;
 20 Ar¹ represents a phenyl group substituted one or more times with alkyl, alkenyl,
 alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and
 R represents a group (Ar²) which is a mono- or polycyclic, heterocyclic group
 other than imidazolyl, which carbocyclic or heterocyclic group may optionally be
 substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino,
 25 halogen, haloalkyl, nitro and/or cyano; or
 R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-
 alkenyl or halo-alkynyl; and
 R¹ and R², independently of each another, represent hydrogen, alkyl, cycloalkyl
 or cycloalkyl-alkyl; or
 30 R¹ and R² together with the phosphor and the oxygen atoms to which they are
 bound form a 5- to 7-membered heterocyclic ring.

44. The chemical compound of claim 43, wherein
 m is 1;
 35 n is 0 or 1;

X and Y, independently of each another, represent halogen, alkyl, CF₃, nitro and/or cyano;

Ar¹ represents a phenyl group substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

5 Ar² represents an aromatic group selected from phenyl, 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or
10 twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

R¹ and R², independently of each another, represent alkyl, cycloalkyl or cycloalkyl-alkyl; or

15 R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a 5-to 6-membered heterocyclic ring.

45. The chemical compound of claim 44, wherein

m is 1;

20 n is 0 or 1;

X and Y, independently of each another, represent fluoro, chloro, CF₃, nitro and/or cyano;

Ar¹ represents phenyl, substituted once or twice with fluoro, chloro, CF₃, nitro and/or cyano;

25 Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic group optionally may be substituted once or twice with fluoro, chloro, methyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or halo-alkyl; and

30 R¹ and R², independently of each another, represent alkyl, cycloalkyl or cycloalkyl-alkyl; or

R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a 5-membered heterocyclic dioxaphospholane ring.

46. The chemical compound of claim 45, wherein

35 m is 1;

n is 0 or 1;

X and Y, independently of each another, represent fluoro, CF₃, nitro and/or cyano;

Ar¹ represents phenyl, which is substituted once or twice with fluoro, CF₃, nitro and/or cyano;

Ar² represents phenyl or 2-thiazolyl, which aromatic group may optionally be substituted once or twice with fluoro, methyl, CF₃, nitro and/or cyano; or

5 R represents alkyl, cycloalkyl or cycloalkyl-alkyl; and

R¹ and R², independently of each another, represent alkyl or cycloalkyl; or

R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a 5-membered heterocyclic dioxaphospholane ring.

10 47. The chemical compound of claim 46, which is

[Cyclohexyl-bis-(4-fluorophenyl)-methyl]-phosphonic acid dimethyl ester;

[Cyclopentyl-bis-(4-fluorophenyl)-methyl]-phosphonic acid dipropyl ester;

[1,1-Bis-(4-fluorophenyl)-hexyl]-phosphonic acid dimethyl ester;

[1,1-Bis-(4-fluorophenyl)-2-methyl-propyl]-phosphonic acid dimethyl ester;

15 [Bis-(4-fluorophenyl)-pyridin-2-yl-methyl]-phosphonic acid dimethyl ester;

[Bis-(4-fluorophenyl)-thiazol-2-yl-methyl]-phosphonic acid dimethyl ester;

[Tris-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester;

[(2-Fluoro-phenyl)-bis-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester;

20 [(2-Chloro-phenyl)-(2-fluoro-phenyl)-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester;

[(4-Chloro-phenyl)-bis-(4-fluoro-phenyl)-methyl]-phosphonic acid dimethyl ester;

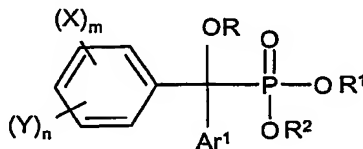
[Bis-(4-fluoro-phenyl)-(2-fluoro-phenyl)-methyl]-phosphonic acid; or

[Bis-(4-fluoro-phenyl)-*p*-tolyl-methyl]-phosphonic acid;

any of its enantiomers or any mixture of enantiomers, or a pharmaceutically

25 acceptable salt thereof, or an N-oxide thereof.

48. The chemical compound of claim 1, represented by the following Formula XII (Type 12)



30 wherein

m is 0, 1 or 2;

n is 0, 1 or 2;

X and Y, independently of each another, represent alkenyl, alkynyl, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

35 Ar¹ represents a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more

times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; and

R represents a group (Ar^2) which is a mono- or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic group optionally may be substituted one or more times with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R^1 and R^2 , independently of each another, represent hydrogen, alkyl or alkoxy; or

R^1 and R^2 together with the phosphor and the oxygen atoms to which they are bound form a heterocyclic (dioxaphospholane) ring.

49. The chemical compound of claim 48, wherein

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, CF_3 , nitro and/or cyano;

Ar^1 represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano;

Ar^2 represents an aromatic group selected from phenyl; 2, 4 or 5-thiazolyl; isothiazolyl, in particular 3, 4 or 5-isothiazolyl; imidazolyl, in particular 1, 2 or 4-imidazolyl; oxazolyl, in particular 2, 4 or 5-oxazolyl; isoxazolyl, in particular 3, 4 or 5-isoxazolyl; pyridinyl, in particular 2, 3 or 4-pyridinyl; pyrimidinyl, in particular 2, 4 or 5-pyrimidinyl; and pyrrolyl (azolyl), in particular 1, 2 or 3-pyrrolyl; which aromatic group may be substituted once or twice with alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino, halogen, haloalkyl, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R^1 and R^2 , independently of each another, represent hydrogen, alkyl or alkoxy; or

R^1 and R^2 together with the phosphor and the oxygen atoms to which they are bound form a heterocyclic (dioxaphospholane) ring.

50. The chemical compound of claim 49, wherein

m is 0 or 1;

n is 0 or 1;

X and Y, independently of each another, represent halogen, CF₃, nitro and/or cyano;

Ar¹ represents phenyl, which may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano;

Ar² represents an aromatic group selected from phenyl, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 2-oxazolyl and 2-pyridinyl, which aromatic groups may be substituted once or twice with halogen, alkyl, CF₃, nitro and/or cyano; or

R represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, halo-alkyl, halo-alkenyl or halo-alkynyl; and

R¹ and R², independently of each another, represent hydrogen, alkyl or alkoxy; or R¹ and R² together with the phosphor and the oxygen atoms to which they are bound form a heterocyclic (dioxaphospholane) ring.

51. The chemical compound of claim 50, which is

[Bis-(4-fluorophenyl)-isopropoxy-methyl]-phosphonic acid dimethyl ester;
[(2-Fluorophenyl)-(4-fluorophenyl)-isobutoxy-methyl]-phosphonic acid dimethyl ester;

[(3-Fluorophenyl)-(4-fluorophenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dimethyl ester;

2-[Bis-(4-fluorophenyl)-isopropoxy-methyl]-[1,3,2]-dioxaphospholane 2-oxide;
[Cyclohexyl-(4-nitro-3-trifluoromethyl-phenyl)-(pyridin-2-yloxy)-methyl]-phosphonic acid dimethyl ester;

[Cyclohexyl-(4-fluorophenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dipropyl ester;

[(4-Chlorophenyl)-(4-fluorophenyl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dimethyl ester;

[1-(3,4-Dichlorophenoxy)-1-(4-fluorophenyl)-hexyl]-phosphonic acid dimethyl ester;

[1-(4-Fluorophenyl)-2-methyl-1-(4-nitro-3-trifluoromethyl-phenoxy)-propyl]-phosphonic acid dimethyl ester;

[(4-Fluorophenyl)-(6-fluoropyridin-2-yloxy)-(4-nitro-3-trifluoromethyl-phenyl)-methyl]-phosphonic acid dimethyl ester;

[(3,4-Dichlorophenyl)-(6-fluoropyridin-3-yloxy)-thiazol-2-yl-methyl]-phosphonic acid dimethyl ester; or

[(4-Fluorophenyl)-(1-methyl-1*H*-imidazol-2-yl)-(4-nitro-3-trifluoromethyl-phenoxy)-methyl]-phosphonic acid dimethyl ester;

any of its enantiomers or any mixture of enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

52. A pharmaceutical composition comprising a therapeutically effective amount of a chemical compound of claims 1-51, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.
53. Use of a chemical compound of any of claims 1-51, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a medicament.
54. The use according to claim 53, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of SK_{Ca} and/or IK_{Ca} channels.
55. The use according to claim 54, which disease, disorder or condition is responsive to inhibition of SK_{Ca} and/or IK_{Ca} channels.
56. The use according to claim 55, which disease, disorder or condition relates to reduction or inhibition of undesired immune-regulatory actions, including graft vs. host syndrome, transplant rejection, or transplant rejection.
57. The use according to claim 56, for the manufacture of a pharmaceutical composition, which further comprises a pharmaceutically effective amount of a conventional immune suppressing agent.
58. The use according to claim 57, wherein the conventional immune-suppressing agent is Amphotericin, Busulphan, Co-trimoxazole, Chlorambucil, colony stimulating factors, corticosteroids, Cyclophosphamide, Fluconazole, folinic acid, Ganciclovir, antilymphocyte immunoglobulins, normal immunoglobulins, Methotrexate, Methylprednisolone, Octreotide, Oxpentifylline, Tacrolimus (FK506), Thalidomide, Zollimomab aritox, or the calcineurin inhibitors (protein phosphatase 2B inhibitors), in particular Cyclosporin.
59. A method for of treatment, prevention or alleviation of a disease or a disorder or a condition responsive to modulation of SK_{Ca} and/or IK_{Ca} channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a chemical compound of any of claims 1-51.

60. The method according to claim 59, wherein the disease, disorder or condition is responsive to inhibition of SK_{Ca} and/or IK_{Ca} channels.
61. The method according to claim 60, wherein the disease, disorder or condition
5 relates to reduction or inhibition of undesired immune-regulatory actions, including graft vs. host syndrome, transplant rejection, or transplant rejection.
62. The method according to claim 61, which method comprises simultaneous
10 administration of a pharmaceutically effective amount of a conventional immune suppressing agent.
63. The method according to claim 62, wherein the conventional immune-suppressing agent is Amphotericin, Busulphan, Co-trimoxazole, Chlorambucil, colony stimulating factors, corticosteroids, Cyclophosphamide, Fluconazole,
15 folinic acid, Ganciclovir, antilymphocyte immunoglobulins, normal immunoglobulins, Methotrexate, Methylprednisolone, Octreotide, Oxpentifylline, Tacrolimus (FK506), Thalidomide, Zolimomab aritox, or the calcineurin inhibitors (protein phosphatase 2B inhibitors), in particular Cyclosporin.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00004

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C323/00 C07C317/00 C07C271/06 C07C333/02 C07D227/22
C07D213/28 C07D295/16 C07F9/02 A61K31/27 A61K31/66
A61K31/426 A61K31/395 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 818 030 A (PIEMPEL M ET AL) 18 June 1974 (1974-06-18) the whole document	1-11, 43-53
X	--- DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS accession no. 1990:424044, document no. 113:24044; SHI, MIN ET AL: "Photolysis of (triarylmethyl)phosphonic acids and their esters" XP002236390 & Bulletin of the Chemical Society of Japan (1990), 63(2), 453-60 --- -/-	1-11, 43-51

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

28 March 2003

Date of mailing of the international search report

19. 05. 2003

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS accession no. 1976:586586, document no. 85:186586; KESSEL, DAVID ET AL: "Effects of S-(trityl)-L-cysteine and its analogs on cell surface properties of leukemia L1210 cells" XP002236391 & Biochemical Pharmacology (1976), 25(16), 1893-7</p> <p>---</p>	<p>1-11, 18-22, 52,53</p>
X	<p>DHAR T G ET AL: "Design, synthesis and evaluation of substituted triarylnipeptotic acid derivatives as GABA uptake inhibitors: identification of a ligand with moderate affinity and selectivity for the cloned human GABA transporter GAT-3." JOURNAL OF MEDICINAL CHEMISTRY. UNITED STATES 22 JUL 1994, vol. 37, no. 15, 22 July 1994 (1994-07-22), pages 2334-2342, XP002236387 ISSN: 0022-2623 the whole document</p> <p>---</p>	<p>1-12, 18-22, 52,53</p>
X	<p>WO 00 69439 A (OLESEN SOEREN PETER ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK) 23 November 2000 (2000-11-23) the whole document</p> <p>---</p>	<p>1-63</p>
X	<p>US 5 070 087 A (TENG LINA C ET AL) 3 December 1991 (1991-12-03) the claims column 21-22</p> <p>---</p>	<p>1-12, 18-22, 52,53</p>
X	<p>WO 01 49663 A (UNIV CALIFORNIA) 12 July 2001 (2001-07-12) the whole document</p> <p>---</p>	<p>1-63</p>
X	<p>WO 97 34599 A (CHILDRENS MEDICAL CENTER) 25 September 1997 (1997-09-25) the claims</p> <p>---</p>	<p>1-63</p>
X	<p>WO 01 30327 A (AVENTIS PHARMA GMBH) 3 May 2001 (2001-05-03) the claims page 6, line 21-25</p> <p>---</p>	<p>1-63</p>
X	<p>WO 00 50026 A (MCNAUGHTON SMITH GRANT ANDREW ;STOCKER JONATHAN WALTER (US); ICAGE) 31 August 2000 (2000-08-31) the whole document</p> <p>---</p>	<p>1-63</p>
	<p>---</p> <p>-/--</p>	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 34589 A (ION PHARMACEUTICALS INC ;HARVARD COLLEGE (US); CHILDRENS MEDICAL C) 25 September 1997 (1997-09-25) the whole document ---	1-63
X	WO 00 06137 A (ABBOTT LAB) 10 February 2000 (2000-02-10) the whole document ---	1-63
A	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS accession no. 1997:221960, document no. 126:317085; MAHARAJH, RABINDRANATH B. ET AL: "Synthesis high-field NMR, x-ray structure, and conformational analysis of a 10-membered diamide disulfide ring" XP002236392 RN 189338-80-5 abstract & Canadian Journal of Chemistry (1997), 75(2), 140-161 ---	1-11, 13-17, 38-42
A	CHARLES R. WILLIAMS ET AL: "Unexpected Catalytic Sulfur Extrusion in the Reaction of Triphenylmethanesulfonyl Chloride with Thiocarbonyls" TETRAHEDRON LETTERS, vol. 32, no. 52, 1991, pages 7633-7636, XP002236388 the whole document ---	1-11, 18-22
A	JIAN WU ET AL: "Asymmetric Anionic Polymerization of (2-Fluorophenyl)(4-fluorophenyl)(2-pyridyl)methyl Methacrylate Leading to a Helical Polymer" JOURNAL OF POLYMER SCIENCE: PART A: POLYMER CHEMISTRY, vol. 36, no. 12, 1998, pages 2013-2019, XP002236389 page 2014 page 2015 -----	1-51

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 59-63
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-63 all in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 59-63

Claims 59-63 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Continuation of Box I.2

Claims Nos.: 1-63 all in part

Present claims 1-63 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, the search has been carried out for those parts of the application which appear to be clear and concise, namely mainly those compounds being tertiary triaryl derivatives recited in the examples in the description at page 49, compounds 1 to 3, page 54, compounds 4-1 to 4-12, page 57, compounds 5-1 to 5-13, page 59, compounds 5-14, 5-16 to 5-21, page 61, compounds 6-1 to 6-12, page 63, compounds 7-1 to 7-14, page 65, compounds 8-1 to 8-12, page 67, compounds 9-1 to 9-12, and pages 69-70, compounds 10-1 to 10-7, and 10-10 to 10-15, and closely related homologous compounds. Confer claims 8 (page 80, line 20-line 23), 17, 22, 27, 32, 37, 42 and 47 (line 10-line 12 and line 15-line 25).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00004

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3818030	A	18-06-1974	DE 2140865 A1	15-03-1973
			AT 311997 B	10-12-1973
			AU 468532 B2	15-01-1976
			AU 4553172 A	21-02-1974
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			CH 575959 A5	31-05-1976
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